THE TREATMENT OF OBESITY BY THE "HIGH-FAT" DIET

THE INEVITABILITY OF CALORIES

JOHN YUDKIN
M.A., M.D., Ph.D. Cantab., M.R.C.P., F.R.I.C.
PROFESSOR OF NUTRITION IN THE UNIVERSITY OF LONDON AT QUEEN ELIZABETH COLLEGE, LONDON, W.8

MARGARET CAREY
B.Sc. Lond.
CHIEF DIETITIAN, ST. GEORGE'S HOSPITAL, LONDON, W.1

THE difficulties in treating obesity lie not so much in that we do not know what to do, but that we do not know very well how to do it. What we have to do is to persuade the patient to eat less; it is in this that we often fail. One of the causes of failure is that the conventional low-calorie diets, restricted in both fat and carbohydrate, usually lead to hunger which the patient is unable, or unwilling, to tolerate.

In the last few years, many have found that diets restricted in carbohydrate only, and not in fat, give satisfactory weight-reduction without hunger (e.g., Yudkin 1958). Since these diets allow unlimited protein and fat, they are sometimes referred to as high-fat diets rather than low-carbohydrate diets. Understandably, the phrase "high-fat" in relation to weight-reduction is sufficiently startling to have made a deep impression both on the public and on the medical profession (see for example correspondence in the *British Medical Journal* in early 1959). Superficially, it appears that a diet which makes an obese person lose weight whilst allowing him unlimited fat refutes the orthodox contention that weight-loss can only be achieved by caloric restriction. This refutation of the orthodox rests on the idea put forward by Pennington (1953a) that obese people gained weight because of a metabolic defect. They were said to be unable to metabolise carbohydrate completely, so that it was oxidised only as far as pyruvic acid. This was supposed to inhibit fat oxidation and stimulate fat synthesis. Severe restriction of dietary carbohydrate would lead to mobilisation of body-fat, even in the presence of large amounts of dietary fat.

Later reports by Kekwick and Pawan (1953, 1956) were taken by many to support this view. These authors gave obese patients diets of 1000 calories, in which 90% of the calories came either from protein, or from fat, or from carbohydrate. During the 8 or 10 days in which the patients ate the diets, they lost most weight with the fat diet; and lost little or none, or even gained it, with the carbohydrate diet. Kekwick and Pawan (1956) suggested that "obese patients must alter their metabolism in response to the contents of the diet".

These conclusions, however, are unlikely, and extrapolation from them (e.g., by Mackarness 1958) unwarranted. As long ago as 1932, Lyon and Dunlop had obtained similar results and, quite reasonably, explained them as being due to variation in loss or retention of fluid. The results of Kekwick and Pawan were obtained on patients given the various diets for only a few days. It was clearly necessary to repeat these experiments for longer periods. This was done by Pilkington and his colleagues (1960), who studied the effect of similar diets for periods of 18 or 24 days. Although the first few days on each diet gave the same sort of results as those of Kekwick and Pawan, there was after this a steady rate of weight-loss, which was the same with each diet. They concluded that temporary differences with the different diets were due mainly to changes in fluid-balance. Olesen and Quaade (1960) reached the same conclusions.

It seems then fairly certain that, apart from these initial differences, a calorically restricted diet leads to weight-loss in the obese which is independent of the source of calories. This makes it unlikely that the "high-fat" diet recommended for the treatment of obesity owes its effectiveness to some peculiarity in metabolism.

The alternative explanation is that the "high-fat" diet leads to weight-loss because, in spite of its unrestricted allowance of fat and protein, it is in fact a low-calorie diet. This was the explanation that one of us had already put forward (Yudkin 1958). Such a view is simple and orthodox, and therefore unspectacular. This is probably one of the reasons why many have preferred to accept the more exciting theories based on some postulated but unproven defect in metabolism. Yudkin (1958) pointed out that a diet severely restricted in carbohydrate would, if anything, also be somewhat reduced in fat. Thus, restriction of bread is likely to lead to a lower intake of butter. Restriction of ice-cream, cakes, and most biscuits restricts not only the carbohydrate they contain but also the fat.

These considerations, however, are still theoretical. Pennington (1953b) stated that his subjects lost weight on low-carbohydrate diets containing 3000 calories or more, but gave no indication of their previous diet, or quantitative details of their low-carbohydrate diet. The experiments we describe were undertaken to ascertain the effect of a restriction of carbohydrate on the intake of calories, fat, and protein.

The Investigation

We have studied six adult subjects. Four were nursing sisters, and the other two were the father and brother of one of them. Apart from their overweight, all were apparently healthy and were working during the time of the investigation. They were carefully instructed by one of us in the weighing and recording of their complete diets. They were told to eat their usual foods for 2 weeks. At the end of this time, they were asked to reduce the carbohydrate in their diets to about 50 g. daily for a further 2 weeks, and to eat as much protein and fat as they liked. They were given a list of foods containing carbohydrate in significant amounts, and told that they could eat unlimited amounts of such foods as meat, fish, eggs, cheese, butter, margarine, and cream. They were not asked to restrict water or salt. They weighed themselves daily, at the same time, throughout the 4 weeks of the test.

From the daily dietary records, we calculated the intake of calories, protein, fat, and carbohydrate. As far as possible, we used the tables of McCance and Widdowson (1946); for some proprietary foods, we obtained analytical figures from the manufacturers.

TABLE I—EFFECT OF "HIGH-FAT" DIET ON INTAKE OF CALORIES. AVERAGE DAILY INTAKE OVER TWO WEEKS

Subject	Height (ft. in.)	Weight (lb.)	Weight loss (lb.)	Daily caloric intake	
				"Normal"	"High-fat"
1 (M)	5 11½	189	9	3450	1550
2 (M)	5 9	215	8	2900	1600
3 (F)	5 6½	149½	6	2600	1350
4 (F)	5 2	169	5	2000	1250
5 (F)	5 3	167	6½	1600	1250
6 (F)	5 4½	142*	2†	1500	1300

* After loss of 3 lb. during 2 weeks on normal diet.
† Loss in 12 days on "high-fat" diet.

Results

In all subjects the caloric intake fell significantly during the time they were eating the low-carbohydrate diet (table I). The reduction in calories ranged from 200 to 1900 a day, or from 13% to 55% of the original calories. These changes were all statistically significant at the 5% level, or better.

During the initial 2 weeks, five of the subjects did not change weight by more than 1 lb. Subject no. 6 lost 3 lb., and was clearly restricting her intake of food during this preliminary period. In the next 2 weeks, on the carbohydrate-restricted diet, all the subjects lost weight. Subject no. 6 kept records for only 12 days in this period, during which she lost another 2 lb. The other subjects lost from 5 lb. to 9 lb. in 14 days. The loss in weight was, with only one exception, proportional to the decrease in calories.

In spite of the loss of weight, and in spite of the reduction in calories—in some instances considerable—none of the subjects complained of hunger, though two reported an urge to eat foods containing sugar or starch. This is in line with our previous experience with more than a hundred subjects (Yudkin 1959). The implications of this observation are discussed later.

All the subjects substantially reduced their intake of carbohydrate, as they were requested to do (table II). With their normal diets, they had consumed between about 140 g. and 500 g. carbohydrate as a daily average; on a carbohydrate-restricted diet, they reduced these amounts to between 30 g. and 55 g.

In five subjects, the protein intake was not affected by the changed diet. The exception was subject no. 6, who had been eating a restricted diet during the preliminary 2 weeks. When told to restrict carbohydrate and eat as much fat and protein as she wished, she ate significantly more protein than before—a daily average of 72 g. compared with 57 g.

None of the six subjects showed a significant increase in the amount of fat consumed. Three of them in fact showed a significant reduction of fat, varying from 22 g. to 35 g. daily.

Discussion

We have assessed dietary intake by records of the subjects' weighing of their food, and the conversion of this into terms of nutrients from the food tables. There are several ways in which this method may be inaccurate (Chappell 1955). However, each subject was weighing his diet himself both during the preliminary period and during the experimental period. Since we were interested mainly in the changes in dietary intake between these two periods, many of the possible sources of absolute error in the methods we have used will be similar in both periods and so may be ignored. One source of error, however, is inherent in any investigation of this sort, and that is the change of the diet by the subject himself because he is under observation. This probably accounts for the low caloric intake of subject no. 6 during the preliminary period. That she lost weight during this time makes it certain that she normally ate more than this. It is likely that her normal diet consisted simply of more food, and so contained more protein, fat, and carbohydrate.

The main purpose of this investigation was to find out what happened to the intake of calories, and of protein and fat, in diets considerably restricted in carbohydrate. The answer seems unequivocal; there was a reduction in calories, no significant change in protein, and either no significant change, or else a reduction, in fat.

These results show that the term "high-fat diet" is a misnomer; the correct term is "low-carbohydrate diet". We now also understand why this diet can lead to loss of weight in the obese. It is low in calories, and it is this which causes loss of weight, and not some peculiarity in carbohydrate metabolism. Nevertheless, the origin of the term "high-fat diet" is understandable. Firstly, orthodox diets for weight-reduction restrict fat, but the low-carbohydrate diet allows unrestricted fat. Secondly, since the total intake of calories is restricted, the *proportion* coming from fat is usually increased. Thirdly, and most important, the term "high-fat" derives from the confusion between "unrestricted" and "unlimited". Attention has already been drawn to this (Yudkin 1959), when it was pointed out that "as much as you like" means only what it says. It means as much as a person wants to take, and not vast and unlimited amounts. As we see, in diets with restricted carbohydrate,

TABLE II—EFFECT OF "HIGH-FAT" DIET ON INTAKE OF PROTEIN, FAT, CARBOHYDRATE, AND CALORIES. AVERAGE DAILY INTAKE IN GRAMMES, ± STANDARD DEVIATION

Subject	Diet	Calories		Carbohydrate		Protein		Fat	
		±S.D.	Difference and significance	g. ±S.D.	Difference and significance	g. ±S.D.	Difference and significance	g. ±S.D.	Difference and significance
1	Normal	3460±547	−1920[c]	495±114	−425[c]	106±17·7	−6 N.S.	126±29·2	−22[a]
	High-fat	1540±331		43± 7·5		100±21·9		104±26·6	
2	Normal	2900±444	−1280[c]	345±63·2	−290[c]	95±16·8	+10 N.S.	131±29·2	−25[a]
	High-fat	1620±319		55±10·7		105±20·9		106±22·8	
3	Normal	2580±304	−1240[c]	285±58·0	−236[c]	78±14·3	−3 N.S.	127±16·2	−35[c]
	High-fat	1340±259		49± 8·3		75±16·7		92±17·4	
4	Normal	1990±427	−730[c]	212±62·4	−182[c]	67±10·0	+3 N.S.	99±23·0	−7 N.S.
	High-fat	1260±213		30± 6·5		70±11·8		92±18·1	
5	Normal	1610±308	−340[c]	156±35·9	−113[c]	58±10·5	+1 N.S.	85±22·4	+6 N.S.
	High-fat	1270±274		43±12·7		59±11·4		91±25·5	
6	Normal	1480±301	−180[a]	138±39·1	−96[c]	57±14·5	+15[a]	78±21·4	+14 N.S.
	High-fat	1300±175		42± 6·1		72±18·0		92±21·0	

Significance: N.S., not significant; [a], $P<0.05$; [c], $P<0.001$.

"as much as you like" of fat turns out to be no more fat than before, and sometimes even less.

In our subjects, the carbohydrate intake was reduced considerably. We do not know whether all obese subjects need such drastic reduction in order to lose weight. It should, however, be noted that half a pint of milk and reasonable helpings of green vegetables will give some 25 g. or 30 g. of carbohydrate. In order to keep carbohydrate intake at a low level, it is important that the patient be told that glucose or sorbitol should not be taken as alternatives for sugar. He should be told also that bread substitutes, in spite of the claims made for them, do not necessarily contain a significantly lower amount of carbohydrate than bread. In this connection, we have had some analyses made of the commoner bread substitutes, and have found that most of those consumed by the obese give them (besides a feeling of self-righteousness) a great deal of carbohydrate.

The results we have reported raise a problem in relation to control of appetite, at least in the obese. Current theories assume that appetite is controlled chiefly, if not entirely, by calories; explicitly or implicitly they give equal values to calories from protein, fat, and carbohydrate. Yet we have seen that a change to a low-carbohydrate diet may in the obese reduce calories to half or less, but may not lead to hunger. So long as it was thought that the diet was high in fat, it might have been postulated that this was responsible for the satiety (*Lancet* 1960). But the diet is not high in fat, contains significantly fewer calories, and is nevertheless satiating. We can appreciate this surprising fact—and, perhaps, derive a clue towards explaining it—if we consider the situation in reverse. An obese person is consuming a low-carbohydrate diet which gives him, say, 2000 calories, derived mostly from protein and fat. On this diet he is quite satisfied. He now adds an amount of carbohydrate which gives him 1000 or so additional calories. If his appetite were controlled entirely by calories, he would consume less of the other foods to the extent of the same 1000 calories. But he does not do this; in fact, he is likely, in addition to his 1000 extra calories from carbohydrate, to take more fat as well.

It would seem from this that carbohydrate does not satisfy the appetite; it may even increase it, because more dietary carbohydrate may lead to more dietary fat. This conclusion is supported by the observation that the addition of glucose to a reducing diet led to a decreased loss of weight; this could not be accounted for by the calories from the glucose, and suggests that the glucose stimulated the appetite (Yudkin 1959).

These considerations are derived from a restricted study with obese subjects. We wish to stress that the conclusions which can be drawn from them must at present also be restricted.

Firstly, there is presumably a limit to the amount of carbohydrate which one can eat without reaching satiety. It is likely that this limit varies with different individuals, and it may be that the varying extent of "excessive" consumption in our six subjects is an indication of the variation in the satiety value of carbohydrate for different individuals.

Secondly, we do not know whether these conclusions apply only to obese persons. If they do, it is possible to imagine that this signifies a major and qualitative difference between the obese and the non-obese; the obese may be those in whom carbohydrate does not easily satisfy the appetite. This is similar to the suggestion made by Beaudoin et al. (1953). On the other hand, if this property of carbohydrate is common to all people, though perhaps in varying degrees, it should be possible to make thin people put on weight by increasing dietary carbohydrate. Ordinary dietary recommendations, which usually involve an increase in foods such as butter and cream, are often notoriously ineffective in increasing the weight of thin people.

Thirdly, we have spoken of carbohydrate as if all forms behave in the same way. For this, we have no evidence. It may well be, for example, that sugars, which are rapidly absorbed, behave differently from starches. This, and the other questions raised in this discussion, cannot be answered without further investigation.

Summary

A study has been made of the intake of calories, protein, fat, and carbohydrate of six obese subjects before and during the consumption of a "high-fat" diet. For this diet, the subjects were instructed to limit only carbohydrate, and to consume as much fat and protein as they wished. All subjects lost weight during the 2 weeks on the diet. Their daily intake of calories was found to be from 200 to 1900 lower, a reduction of between 13% and 55%. No subject consumed significantly more fat than before; three subjects consumed significantly less.

Thus, the term "high-fat" diet is wrong; it should be "low-carbohydrate" diet. The obese patient loses weight on this diet, not because of some peculiar metabolism of fat but because of a reduction in calories. The implications of these findings are discussed in relation to theories of appetite control.

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ABSORPTION, EXCRETION, AND RETENTION OF STRONTIUM BY BREAST-FED AND BOTTLE-FED BABIES

ELSIE M. WIDDOWSON, D.Sc. Lond.
JEAN E. SLATER, Ph.D. Cantab., B.Sc. Lond.
OF THE MEDICAL RESEARCH COUNCIL DEPARTMENT OF EXPERIMENTAL MEDICINE, UNIVERSITY OF CAMBRIDGE
G. E. HARRISON, D.Sc. Birm., F.Inst.P.
ALICE SUTTON, Ph.C.
OF THE MEDICAL RESEARCH COUNCIL RADIOBIOLOGICAL RESEARCH UNIT, HARWELL

THE amount of strontium in the bones of newborn babies has been studied in recent years, and analyses of bones of older babies, of children, and of adults have also been made (Bryant et al.1958, Thurber et al. 1958, Bryant et al. 1959). The average ratio of strontium, measured in microgrammes, to calcium, measured in milligrammes

$$\text{i.e., } \frac{\text{strontium} \times 10^3}{\text{calcium}}$$

in the bones of British babies was found to be about 0·19 at birth, and this ratio was shown to reach the adult level of about 0·3 after 18 years (Bryant et al. 1958). At all

ages, however, the results were somewhat variable, depending no doubt partly upon the amount of strontium in the food. Values for bones of individual babies during the first 6 months were sometimes higher or sometimes lower than the average at birth, and the evidence is insufficient to say whether a rise occurs in the suckling period. There is no doubt, however, that babies are born with strontium in their skeletons, and if Widdowson and Spray's (1951) figure of 28 g. is taken for the average amount of calcium in the body of a fullterm baby at birth, then the amount of strontium must be just over 5 mg.

There is evidence to show that the adult body discriminates against strontium in favour of calcium (Harrison et al. 1955, Comar et al. 1957, Laszlo and Spencer 1958). It has been demonstrated that the ratio of strontium to calcium absorbed from the intestine is always lower than the ratio in the diet, and further, the ratio of strontium to calcium excreted in the urine is higher than the ratio in the plasma or in the bones, and presumably higher therefore than the ratio in the body as a whole. The metabolism of strontium in children between 4 and 14 years has recently been studied (Bedford, Harrison, Raymond and Sutton 1960), and it appears that by the age of 14 the relation between the turnover of strontium and calcium is similar to that in adult life.

Cow's milk contains about six times as much strontium as human milk, but no previous studies have been made of how the strontium of milk is metabolised. The present investigation concerns week-old babies who were having only breast milk or only a cow's milk preparation. We originally hoped to make determinations of strontium-90, but, because the total amount of urine and fæces passed by a baby in the experimental period contained insufficient strontium-90 for one determination, the study was of necessity limited to the stable element.

Subjects and Methods

Nine breast-fed and nine bottle-fed baby boys were studied in the main investigation. They were all born at the Maternity Hospital, Mill Road, Cambridge. The days chosen for study were the 6th, 7th, and 8th after birth, by which time the flow of breast milk was established. Only those babies who had been and still were fully breast-fed were included in the first group. The others had had nothing but a cow's milk preparation since birth. The breast-fed babies, whose average weight during the study was 3·4 kg., were weighed accurately before and after each of the fifteen feeds during the 3 days, and their intake of milk was obtained by difference. Milk was collected from each mother and analysed, and samples were taken from fifteen other mothers as well to gain more information about the amount of strontium in breast milk.

The bottle-fed babies, whose average weight was 3·6 kg., received a preparation made from dried whole cow's milk and lactose. A special batch was made for us by the manufacturers, and this was used for the first six babies. We then found that the commercial cow's milk preparation in general use at the hospital contained twice as much stable strontium as the special preparation, and this was used for the three babies studied during the latter part of the investigation.

For all the bottle-fed babies an amount of milk powder sufficient for one day was accurately weighed out and mixed with a measured volume of distilled water. The mixture was stored in a refrigerator, and portions were transferred to the feeding bottle as required; the bottle was weighed before and after each feed.

The methods used for collecting quantitatively all urine and fæces passed by the babies, and their regurgitated food, have been described by Slater (1961). A carmine marker was given (0·25 g. mixed with a little water in a feeding bottle) before the first feed of the 3-day period and before the first feed on the 4th day. Fæces were collected from the first to the second appearance of the marker.

Portions of the food, urine, fæces, and regurgitated food were dried and ashed at 450°C, the ash was extracted with HCl, and determinations of strontium, calcium, and phosphorus were made on the extract.

TABLE I—STRONTIUM (μG. PER 100 ML.) AND CALCIUM AND PHOSPHORUS (MG. PER 100 ML.) IN BREAST MILK AND THE TWO COW'S MILK PREPARATIONS

Type of milk	Sr	Ca	P
Breast milk:			
Average for mothers whose babies were studied	6·9	27·8	15·6
Pooled sample from 15 other mothers ..	8·7	24·6	15·5
Cow's milk preparation diluted with water			
Analysed as fed to babies:			
Special preparation	26·2	102	76
Commercial preparation	52·5	102	76

Calcium was determined by the Clark and Collip modification of the Kramer and Tisdall method, as described by Economou-Mavrou and McCance (1958), and phosphorus was determined as described by Fiske and Subbarow (1925), after heating a sample of the acid extract of the ash with a few drops of concentrated H_2SO_4 to ensure that all the phosphorus was present as orthophosphate. Strontium was separated as described by Harrison (1958), and determined either by neutron activation (Harrison and Raymond 1955) or by means of a 'Unicam' flame spectrophotometer, using the additive standard method (Harrison 1958).

"Blank" determinations were made on washings from the equipment used to collect the excreta, to ensure that the strontium measured had come from the baby and not from any extraneous source. The amount of strontium in these washings was negligible.

Results

Table I shows the average composition of breast milk from the mothers whose babies were included in this investigation, and of a pooled sample of milk from fifteen mothers at the same stage of lactation. The composition of the two samples of the cow's milk preparation, diluted as they were fed to the babies, is also given. The special cow's milk preparation contained about four times, and the commercial preparation eight times, as

TABLE II—INTAKES, EXCRETIONS, ABSORPTIONS, AND RETENTIONS OF STRONTIUM, CALCIUM, AND PHOSPHORUS BY BREAST-FED AND BOTTLE-FED BABIES

Mean values. Standard errors in parentheses.

—	Intake	Output			"Absorption"	"Retention"
		Urine	Fæces	Total		
Strontium (μg. per kg. per 24 hr.)						
Breast-fed babies	8 (±0·5)	14 (±2·6)	14 (±2·0)	28 (±3·0)	−6 (±1·9)	−20 (±2·9)
Bottle-fed babies:						
Special cow's milk preparation	35 (±1·3)	2 (±0·6)	24 (±2·9)	26 (±2·7)	+11 (±2·7)	+9 (±1·9)
Commercial cow's milk preparation ..	72 (±2·2)	2 (±0·5)	19 (±1·5)	21 (±1·7)	+53 (±3·2)	+51 (±3·0)
Calcium (mg. per kg. per 24 hr.)						
Breast-fed babies	35·7 (±4·1)	5·3 (±0·8)	15·4 (±1·9)	20·7 (±2·1)	20·3 (±3·3)	15·0 (±2·7)
Bottle-fed babies	135 (±4·3)	2·4 (±1·2)	52·8 (±4·6)	55·2 (±4·5)	82·2 (±4·6)	79·8 (±4·7)
Phosphorus (mg. per kg. per 24 hr.)						
Breast-fed babies	19·5 (±1·6)	0·5 (±0·1)	2·2 (±0·3)	2·7 (±0·3)	17·3 (±1·5)	16·8 (±1·5)
Bottle-fed babies	103 (±2·7)	35·2 (±2·1)	17·4 (±1·4)	52·6 (±2·4)	85·6 (±2·9)	50·4 (±3·4)

TABLE III—RELATIVE DIETARY INTAKE AND EXCRETION OF STRONTIUM AND CALCIUM

Results expressed as $\frac{Sr}{Ca} \times 10^3$

Age-group	Intake	Excretion	
		Urine	Fæces
Breast-fed babies	0·2	2·6	0·9
Bottle-fed babies:			
Special cow's milk preparation	0·3	0·8	0·4
Commercial cow's milk preparation	0·5	0·8	0·5
Children aged 4–14 years (Bedford et al. 1960)	..	1·3	1·9
Adults (Harrison et al. 1955)	1·6	0·9	2·3

much strontium as the average amount in the samples of breast milk consumed by the babies in this investigation. The two cow's milk preparations contained identical amounts of calcium and phosphorus, which were four times (calcium) and five times (phosphorus) as high as the concentrations in breast milk.

Table II shows the mean intakes, "absorptions", excretions, and "retentions" of strontium, calcium, and phosphorus by the breast-fed and bottle-fed infants. Standard errors are also given. "Absorption" is calculated as the difference between the amount in the food and the fæces, and "retention" as the difference between the amount in the food and the total output in the urine and fæces together.

The average strontium intakes of the bottle-fed babies having the two different cow's milk preparations were four and eight times as high as those of the babies having breast milk. Despite this, the breast-fed babies excreted about seven times as much strontium in the urine. The breast-fed babies excreted about the same amount of strontium in the urine as they did in the fæces, and in most cases each contained more strontium than the food. These babies were therefore all in strongly negative strontium balance, although they were in positive balance for all other dietary constituents investigated, including calcium and phosphorus.

All babies having the cow's milk preparations were in positive strontium balance. Most of the strontium excreted was lost by way of the bowel, the urinary excretion amounting to only 7–10% of the total in contrast to 50% in the case of the breast-fed babies. The infants given the commercial preparation containing the larger amount of strontium retained five times as much as the babies given the special cow's milk preparation; their urinary excretion was low and their fæcal excretion no higher than that of the other group of bottle-fed babies.

The average intakes of calcium and phophorus by the babies having the special and commercial cow's milk preparations were almost identical, and, since their absorptions and excretions were also very similar, the results for the calcium and phosphorus turnover of all the bottle-fed babies have been averaged together (table II). These findings are discussed in detail elsewhere (Slater 1961); they are only given here so that the metabolism of strontium can be considered in relation to them.

Table III shows the ratio of strontium $\times 10^3$ to calcium in the food and excreta, and results previously obtained for older children and adults are given for comparison. These mean values were obtained by calculating the ratios for each individual baby and averaging them. They give a measure of the body's discrimination against strontium in favour of calcium at different ages. Both types of milk contained much less strontium in relation to calcium than did the adult diet, which is a reflection of the fact that calcium is preferentially secreted in milk. The ratio in breast milk (0·2) was about the same as that in the baby's bones at birth. In the breast-fed babies the ratio of strontium to calcium in the fæces was much higher than that in the food, which shows in another way that calcium was preferentially absorbed, or strontium preferentially secreted in the digestive juices. In the bottle-fed babies having the special cow's milk preparation the fæcal ratio was also a little higher than the ratio in the food, but in the babies having the commercial preparation the ratios were almost the same.

The breast-fed babies had the highest urinary strontium/calcium ratio; the bottle-fed babies excreted less strontium relative to calcium than the older children, and their value was similar to that in adults.

Effect of Additional Phosphate in Breast-fed Babies

We were naturally curious to know why breast-fed babies should be removing strontium from their bones in this way, and in particular why their urinary excretion should be so much higher than that of the bottle-fed babies. A possible reason seemed to be that breast milk contains so little phosphorus. Breast-fed babies excrete only traces of phosphorus in the urine (Widdowson and McCance 1959, and table II), although their kidneys are capable of excreting more if the intake is raised, as it is by cow's milk.

TABLE IV—URINARY EXCRETION OF STRONTIUM, CALCIUM, AND PHOSPHORUS (PER KG. PER 24 HR.) BY BREAST-FED BABIES RECEIVING ADDITIONAL PHOSPHORUS

—	Strontium (μg.)	Calcium (mg.)	Phosphorus (mg.)
Mean value	2·9	2·1	22·9
Standard error	±0·3	±0·7	±1·7

To investigate this point, eight breast-fed babies, with an average weight of 3·3 kg. on the 7th day after birth, were given phosphorus, 120 mg. daily as a 1 to 4 mixture of KH_2PO_4 and Na_2HPO_4, on the 5th, 6th, and 7th days after birth. All the urine passed on the 7th full day after birth was collected and analysed for strontium, calcium, and phosphorus (table IV). Each of the eight babies given phosphates excreted less strontium in the urine than any of the babies getting breast milk alone, and their average excretion of strontium was nearly as low as that of the bottle-fed babies. The urinary excretion of calcium was also reduced, indicating that these two chemically similar elements respond to additional phosphorus in the same way.

Discussion

An unexpected result of this investigation was the high urinary excretion of strontium and calcium by the breast-fed babies, and the way in which this was reduced by the administration of phosphorus. We interpret this as being an indication that the supply of phosphorus was limiting the deposition of minerals in the skeleton. A second surprise was that, although the breast-fed babies were in positive calcium balance, they were in strongly negative strontium balance, and, as already stated, both urine and fæces contained more strontium than the food. The excreted strontium must have been mobilised from the bone salt laid down before birth, and two possible mechanisms might bring this about:

Calcium and strontium are believed to be deposited in the skeleton in the form of hydroxyapatites and carbonates in a complex system of crystal lattices. The loss of strontium from the bones could result from an exchange mechanism whereby

strontium is removed from the surfaces of the crystals of bone mineral, and is replaced by calcium.

Alternatively the growth and remodelling of the bone may be implicated. During remodelling bone salt passes into solution, and it may be that, in the presence of a limited amount of phosphate, the calcium is preferentially redeposited along with exogenous calcium absorbed from the gut.

Both these mechanisms would increase the concentration of strontium in the body fluids, and hence lead to its excretion by the kidney.

McCance and Widdowson (1939), who administered strontium intravenously to themselves, found that the injected strontium was excreted slowly, and only a small fraction of it by the intestine. This has been confirmed, in adults, for the stable element by Harrison et al. (1955), and for strontium-85 by Fraser et al. (1960) and by Bishop, Harrison, Raymond, Sutton, and Rundo (1960). It seems, however, that the intestinal glands of young babies must secrete strontium in the digestive juices in comparatively large amounts, for in eight of the nine breast-fed babies we studied the fæces contained more strontium than did the food. There may also be a similar age difference in the intestinal excretion of iron (Josephs 1934, McCance and Widdowson 1937, Stearns and McKinley 1937).

If the whole skeleton of the newborn baby contains 5 mg. of strontium, and if breast-fed babies continued to lose strontium at the rate observed over the short period of this investigation (20 μg. per kg. body-weight per day), then in less than 3 months they would have no strontium, left inside them. The rate of loss would no doubt decline as the amount in the body fell, but this calculation illustrates the quantities involved. The bottle-fed babies having the commercial cow's milk preparation, on the other hand, would have doubled the amount of strontium in their bodies in a little over a month; they would have increased the calcium by only 17% in the same time.

If the specific activity of strontium-90 is the same in the food as in the body, then, because the radioactive component will behave in the same way as the stable element as regards its absorption and excretion, these results give some indication as to what may be happening to the radioactive element. The baby of today already has some strontium-90 in its bones at birth (Bryant et al. 1959). During the first months of life the main source of strontium-90 for the breast-fed baby is the mother's milk. If the specific activity in the baby's body is the same as, or higher than, the activity in the mother's milk, then the negative balance for stable strontium makes it unlikely that any strontium-90 will be retained so long as the baby is fully breast-fed. Infants having cow's milk preparations containing more strontium-90 than breast milk probably retain a proportion of the strontium-90 along with the stable element. They are therefore likely to have more strontium-90 in their bodies than breast-fed babies because (1) more is ingested, and (2) a higher proportion of the intake is probably retained.

Summary

The amounts of stable strontium, calcium, and phosphorus in the food and excreta of nine breast-fed and nine bottle-fed babies were measured on the 6th, 7th, and 8th days after birth.

All the breast-fed babies excreted more strontium than they ingested. If the excretion had continued at the observed rate, then in about 3 months they would have had no strontium left inside them.

All the babies having cow's milk preparations retained strontium, and the amount retained depended upon the amount in the milk. If the retention had continued at the observed rate, then those having the commercial cow's milk preparation would have doubled the amount of strontium in their bodies in about a month.

The amount of phosphorus in the diet may determine whether strontium is eliminated or retained by the body.

We are grateful to Dr. Douglas Gairdner for allowing us to make these measurements on the babies in his care. We are also indebted to the staff at the Maternity Hospital, Mill Road, Cambridge, for their cooperation, and to Miss E. Colbourn and Miss P. Hennessey for their help in collecting the material. Prof. R. A. McCance first suggested phosphorus as the answer to our problem, and Dr. N. Hatemi made available the samples of urine from babies receiving additional phosphates; we should like to express our thanks to both of them.

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NON-UNION OF UTERINE WOUNDS

ABDEL HAMID BADAWY
M.Ch. Cairo
LECTURER IN OBSTETRICS AND GYNÆCOLOGY, KASR EL AINI HOSPITAL, CAIRO, EGYPT, UNITED ARAB REPUBLIC

ALTHOUGH the overall incidence of rupture of the uterus has much diminished in Egypt thanks to better antenatal and intranatal care, rupture of cæsarean scars has not diminished. This is mainly due to the broadening indications for cæsarean section as the operation became safer.

Case-records

The following 3 cases of ruptured uterus seem worth reporting:

Case 1.—A woman aged 25 years, para 2+1 and 20 weeks pregnant, was admitted to Kasr el Aini hospital as an " acute abdomen " with internal abdominal hæmorrhage. She had an abdominal hysterotomy done for hyperemesis gravidarum a year before admission. At laparatomy a midline perforation 7 cm. long was found in the uterus. A clot was filling the gap between the edges of the perforation, and the placenta was bridging the bottom of the gap. The edges of the perforation were clean with no evidence of recent bruising, except in the subperitoneal layer where there was some ecchymosis. After removal of the fœtus and placenta the edges of the perforation were freshened by excising a strip 3 mm. thick on each side. The wound in the uterus was closed in three layers and the abdomen was closed. The convalescence was uneventful. Histologically the excised strips showed normal muscle/connective-tissue ratio and there was no infiltration by red cells, denoting that distruption of the wound was not recent (see figure).

Probably the wound in the uterus did not unite because of the patient's poor general condition at the time of operation. Only

Section of a strip of uterine wall from the edges of the perforation in case 1: no evidence of recent bruising or laceration in the muscle-fibres.

the peritoneal layer of the uterus united and covered the gaping wound in the muscle. As the uterus became distended by the growing fœtal sac, the placenta which had been bridging the gap started to separate. Bleeding then increased the intrauterine tension so that the peritoneum gave way and the patient felt pain.

Case 2.—A married woman aged 26 years was admitted to Kasr el Aini hospital with a recurrent vesicovaginal fistula, which had appeared for the first time 7 days after a cæsarean section for contracted pelvis. The fistula was repaired successfully 8 months after the operation. This was followed by two abortions each at 3 months. Another pregnancy ended in premature labour at 34 weeks, and a stillborn child was delivered per vaginam. The fistula recurred immediately after delivery. Owing to the big size of the fistula and the fixation of tissues around it, repair was undertaken by a combined vaginal and abdominal approach. During the second abdominal stage a subperitoneal longitudinal unhealed wound occupying the lower two-thirds of the body of the uterus was noted. Dense tissue at the lower end of the wound formed the upper limit of the fistula. The closure of the fistula was completed as the edges of the tear in the uterus were excised and sutured. The patient was cured. She became pregnant again and was delivered by cæsarean section.

This patient had a vertical lower-segment wound which was poorly united. It gave way during the subsequent vaginal delivery but the peritoneum remained intact. The muscle edges of the wound did not reunite. The bladder which was overlying the lower part of the incision also gave way and the fistula recurred.

Case 3.—A married woman aged 28 years, para 3, was admitted for a repeat cæsarean section. An elective cæsarean section was done one week before the expected date of delivery. After opening the abdomen, and dividing the uterovesical peritoneum, a transverse tear 6 cm. long was found in the lower uterine segment apparently at the site of the previous incision. Through the hole the membranes were bulging slightly. The hole was widened and the fœtus delivered. The edges of the hole were trimmed and the wound closed.

This case represents an asymptomatic rupture of a lower-segment scar and it remained asymptomatic throughout the pregnancy since vesico-uterine peritoneum was intact.

Discussion

If a cæsarean section is performed for a permanent indication, such as contracted pelvis, then the decision in a subsequent pregnancy is easy: cæsarean section will always be needed. But if the indication is temporary, such as antepartum hæmorrhage or prolapse of the umbilical cord, then subsequent pregnancies will cause much anxiety to the obstetrician. Left to themselves, most of these mothers can safely be delivered vaginally, but in a few cases the cæsarean wound gapes during pregnancy or labour, and may not produce any symptoms or signs. Thus a surgeon opening the abdomen to do a repeat section in a woman in perfectly good condition, with no pain or tenderness, is faced with a gaping wound in the uterus. Such findings show that the gaping of the wound was not a sudden event; in fact cases 1 and 2 suggest that in the great majority of cæsarean scars which rupture in subsequent pregnancies, the wound edges did not unite and then gaped increasingly in later pregnancies. As Pedowitz and Schwartz (1957) put it, "most dehiscences of cæsarean wounds are conceived in the operating room and they develop during the puerperium. Pregnancy only accentuates the defect".

If the placenta is bridging the defect (as in case 1) then as the defect gapes the placenta separates and hæmorrhage begins, the uterus distends and the peritoneum gives way. In these cases pain begins relatively early in pregnancy.

Another factor promoting rupture of the peritoneum is the onset of labour. Here there is a great difference between lower-segment and upper-segment scars. The peritoneum over the lower segment is the vesico-uterine peritoneum which is loose and thus even if the amniotic sac bulges underneath it, it does not give way. Even the bladder itself may cover the defect. Only during labour when the lower segment is greatly stretched and the intrauterine pressure is much increased may the peritoneum give way. Lane and Reid (1953) found in their series that when an upper-segment scar ruptures, in two-thirds of cases it does so during pregnancy and in only one-third does it manifest itself during labour. On the other hand, a lower-segment scar tends to rupture only during labour.

How can the obstetrician tell which patients have sound scars and which non-united or partially united ones? Among the criteria suggested have been the postoperative course, the type of cæsarean section, the skill of the operator, the type of suture material, the indication for the primary operation, the location of the placenta in the current pregnancy, and the presence of tenderness at the site of the scar.

Attempts to assess directly the integrity of the scar and define its subsequent behaviour have been of two main types:

(1) Routine intrauterine palpation of the previous cæsarean scar immediately after a subsequent vaginal delivery. This examination can detect rupture of the scar during the vaginal delivery before shock develops. Further, the integrity of the scar can be assessed and this can be a guide to the management of future pregnancies. It has however, two drawbacks: first, it can be performed only after taking the risk of a vaginal delivery; second, the uterine walls are so soft after labour that it may be difficult to assess the integrity of the scar.

(2) Routine hysterography after cæsarean section has been tried by Baker (1955) and by Poidevin and Bockner (1958). Lateral radiographs in cases of poor union of the uterine wound show defects in the anterior wall, appearing as sacculations or deformities in the wall. Patients with serious defects are advised to undergo repeat cæsarean section.

I wish to thank Prof. Khalil Mazhar for his kind help.

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ANTIVIRAL ACTION OF INTERFERON IN EMBRYONIC CELLS

ALICK ISAACS M.D. Glasg.
SAMUEL BARON * M.D. New York
From the National Institute for Medical Research, Mill Hill, London, N.W.7

Ho and Enders (1959) made the very interesting observation that Hela cells (a cancerous human cell-line) could be induced to make interferon, which, however, could not be assayed in Hela cells, but only in non-cancerous human cells. More recently, Chany (1960) found similarly that interferon produced in KB cells (of cancerous origin) showed antiviral action in normal cells but only a weak action in KB cells. It is known that interferon-treated cells show increased glycolysis (Isaacs 1960); one possible explanation for this increased glycolysis would be that interferon causes an uncoupling action on oxidative phosphorylation, thus limiting the amount of adenosine triphosphate (A.T.P.) available for viral synthesis. Indirect evidence for this suggestion comes from the observation (Isaacs, Klemperer, and Hitchcock 1960) of a number of points of resemblance between the actions of interferon and those of substances known to uncouple oxidative phosphorylation (e.g., 2, 4: dinitrophenol). The lack of antiviral action of interferon in cancerous cells would then be in line with Warburg's (1956) evidence that cancerous cells can form by *anaerobic* processes all the A.T.P. they require for growth. If this line of reasoning is correct embryonic cells, which resemble cancer cells in showing a high rate of anaerobic glycolysis (Warburg 1956), should show a similar resistance to the antiviral action of interferon during an early stage of their development, and should later assume the behaviour characteristic of cells from adult tissues.

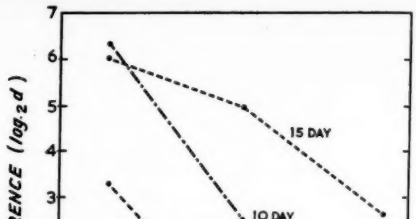
The Experiments

This possibility was investigated by testing the antiviral action of interferon on the growth of influenza virus in pieces of chorioallantoic membrane taken from chick embryos at different stages of their development.

The tissues were treated with interferon in different concentrations and then infected with the PR8 strain of influenza virus. After incubation in a roller-drum the virus yield was measured by the hæmagglutinin titre, and the degree of viral inhibition, or interference, is expressed as the difference between the virus yield in interferon-treated tissues and that of control tissue from embryos of the same age.

It was found that the virus grew equally well in control tissues from embryos of 6, 7, 8, 10, 11, 13, or 15 days. There were striking differences, however, in the sensitivity to interferon of tissues from embryos of different ages. The results of one experiment (see accompanying figure) show that 15-day chorioallantoic membrane pieces are very sensitive to the action of interferon, and significant interference was found with a 1/480 dilution of the interferon preparation used. On the other hand, less viral inhibition was produced by a 16-times greater concentration of the same interferon preparation in 6-day tissues. The 8- and 10-day chorioallantoic membrane pieces showed intermediate sensitivity to interferon, and in this and other experiments there was a gradual, rather than a sudden, acquiring of sensitivity.

Similar experiments with minced embryonic tissue from chick embroys of the same age-group and infected with the parainfluenza 1 (Sendai) or the NWS influenza viruses and incubated with shaking gave essentially similar results. A similar result was also found in an experiment with minced embryonic tissue from mouse embryos of 7 and 18 days; in this experiment encephalomyocarditis virus and interferon prepared in mouse tissues were used.



Degree of interference produced by different amounts of interferon in tissues from chick embryos of 6, 8, 10, and 15 days.

In these experiments the tissues from very young embryos resembled cancer cells in their insensitivity to interferon, but unlike cancer cells, early embryonic cells were found to produce only very low yields of interferon. This was shown by comparing the yield of interferon from 6- and 11- or 13-day chorioallantoic membranes inoculated in vitro with ultraviolet irradiated influenza virus. The 6-day membranes, however, are much smaller than the older membranes, and in order to compensate for these differences pieces of membrane from 6- and 11-day embryos were compared in their ability to produce both virus and interferon. To do this, one group of membranes of each age-group was infected with fully infective influenza virus and the degree of virus multiplication was observed. The second group was infected with ultraviolet irradiated influenza virus and the yield of interferon was measured.

The table shows that the 11-day membranes produced twice as much virus but 20 times as much interferon as the 6-day membranes. (The figure of 20 was obtained by finding that the 11-day interferon had to be diluted about 20 times to give the same degree of inhibition as the 6-day membranes.)

Conclusions

Very young embryos therefore differ from older embryos in being much less sensitive to the antiviral action of interferon, and in producing less interferon on stimulation with ultraviolet-irradiated influenza virus. We have recently found (Isaacs and Hitchcock 1960) that interferon

YIELD OF VIRUS AND INTERFERON FROM 6- AND 11-DAY EMBRYONATED TISSUES

—	Chorioallantic membranes from	
	6-day embryos	11-day embryos
(*a*) Virus yield after infection with influenza virus. (log_2 hæmagglutinin titre)	6·25	7·25
(*b*) Interferon yield after inoculation with irradiated influenza virus. (log_2 d)	4·0	>7·0

6-day and 11-day embryo pieces were inoculated in vitro with (*a*) influenza virus or (*b*) ultraviolet irradiated virus. After 48 hours' incubation at 35°C the virus yield was titrated in (*a*) and the yield of interferon in (*b*). The interferon titre is expressed as the difference between the mean log_2 yield of virus from untreated chick chorioallantoic membrane pieces and from pieces treated with the interferon preparation under test.

* Senior Surgeon, U.S. Public Health Service, at present attached to the National Institute for Medical Research.

may play an important role in recovery from virus infections. If these results hold true for infection of the human embryo the present results would suggest an explanation of the fact that maternal infection with rubella virus during the first 3 months of pregnancy often leads to congenital malformations (Gregg 1941, Swan 1949). Infection after the third month rarely causes congenital malformations. This could be explained by assuming that if the embryo is infected during the first third of the embryonic life, it produces very little interferon and is very insensitive to the antiviral action of interferon, just as occurs in the chick embryo. At a later stage of embryonic development it is presumed that the interferon mechanism comes into play and limits more effectively the viral infection.

These results may have wider implications. We can speculate that the antiviral action of interferon has developed in the course of evolution as an adaptive response to superficial virus infections, such as respiratory virus infections, but that the original function of interferon may have been to play a part in controlling cellular division by controlling the supply of A.T.P. During the first third of embryonic development this mechanism may not become fully established but it may play a more important role thereafter. On this view, the cancer cell is one which has escaped from the control of interferon. These speculations have the advantage that they can be subjected to experimental test.

Summary

Chorioallantoic membranes from 6-day-old chick embryos were much more resistant to the antiviral action of interferon than tissues from older embryos. Similar differences were found in whole chick and mouse embryo minced tissue, and in this respect the behaviour of early embryonic tissue resembles that of cancer cells. Unlike cancer cells, however, cells from 6-day-old chick embryos showed very weak production of interferon.

We should like to thank Mr. V. G. Law and Mrs. V. Clay-Peters for their able technical assistance.

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TWO CASES OF SARCOIDOSIS TREATED WITH MEPACRINE

NILS SÖDERSTRÖM
M.D.

From the Department of Internal Medicine, Karlstad Central Hospital, Karlstad, Sweden

IN certain parts of Scandinavia, sarcoidosis is a major problem. Though some of its symptoms are of little consequence to the patient, it may become a distressing and even fatal affection for which satisfactory therapy is lacking. I feel justified, therefore, in reporting some observations which may indicate a new approach to treatment.

Case-reports

Case 1.—A woman, aged 51, first seen in the outpatient department in November, 1955. She complained of vague involutional symptoms and the routine clinical examination revealed little relevant, except for a peculiar rash, and moderately enlarged, firm, painless lymph-nodes on both sides of the neck.

The rash consisted of groups of medium-sized, firm, brownish-red papules distributed over the face (nose, forehead, and both cheeks). There were similar papules in several places on her back and on her left knee, often arranged in rings around patches of atrophic skin. This rash had been present for more than ten years and had slowly but steadily spread in spite of various forms of treatment.

The histological appearance of a biopsy specimen later proved typical of sarcoidosis, but meanwhile because of the superficial similarity of the exanthem to discoid lupus erythematosus tentative mepacrine treatment (0·1 g. three times daily) was begun. Two weeks later all the skin papules had become converted into atrophic maculæ of a peculiar brownish colour and seemed to be in full regression. The lymph-nodes were smaller but still palpable.

Mepacrine was continued, a dose of 0·1 g. twice daily being given for another fortnight, and 0·1 g. daily for the following two months. During this treatment the papules were replaced by atrophic brown scars: the brown pigmentation slowly disappeared towards the end of the treatment. When the mepacrine was withdrawn, no active manifestation of sarcoidosis could be detected.

The patient did not return until August, 1958. Two new papules had then appeared on her back, but all the skin sarcoids seen in November, 1955, still seemed firmly scarred and inactive.

Case 2.—A woman, aged 30, was admitted in May, 1952, with arthralgia, erythema nodosum, and bilateral hilar lymphoma.

She returned in February, 1953, complaining of headache and impaired nasal breathing. She now had numerous enlarged painless lymph-nodes. Biopsy of a cervical node showed small crowded tuberculoid granulomas typical of sarcoidosis. The nasal mucosa both on the conchæ and on the septum showed a general, firm, nodular swelling which did not respond to decongestives. The findings were said to be typical of sarcoidosis of the nasal mucosa.

During the following years there was a slow centrifugal spread of the cutaneous lesions and new lesions appeared on her right cheek and on her thighs. The nasal obstruction had become disabling. The only effective drugs were the corticosteroids which had to be administered more or less continuously from Nov. 1954 to Oct. 1958, (for most of the time, a maintenance dose of prednisone 5 mg. (three times daily). Every attempt to withdraw the steroids led to an intolerable recurrence of the nasal obstruction. During the steroid treatment, the glandular and skin lesions were suppressed but did not disappear.

Mepacrine treatment was started in Oct. 1958, the dose being 0·1 g. three times daily for the first two weeks, 0·1 g. twice daily for another two weeks, and 0·1 g. daily until the end of Jan. 1959. Mepacrine was not available after this, and the treatment was continued with chloroquine in a dose of 0·25 g. daily, which the patient is still receiving.

The result was spectacular. When the patient returned after three weeks all the skin sarcoids had become tar-brown and atrophic, her nasal breathing was quite free, and the lymph-nodes had disappeared. During the following months, the cutaneous scars contracted and the brown discoloration faded. The steroid dosage (in Oct. 1958, triamcinoline 8 mg. three times daily) was slowly reduced, and the drug was withdrawn in May, 1959, without there being any signs of a recurrence of the sarcoid granulomas.

Discussion

Mepacrine was introduced in 1932 as an antimalarial remedy; during the last war it was found to be a useful drug in the treatment of discoid lupus erythematosus (Prokoptchouk 1940). Since then it seems to have been abandoned for both these diseases and replaced by chloroquine and allied drugs, which probably have a similar action but are less toxic and do not give the same disagreeable pigmentation of the skin.

It is known that mepacrine is taken up preferentially by cells in the lungs, in the liver, in the spleen, and even in

the kidney, and that it may be retained in the cells for a considerable time after the withdrawal of the drug.

The strong brown discoloration of the cutaneous sarcoids in the present cases indicates that mepacrine may have a specific affinity for the cells of sarcoid granulomas. This observation, together with their surprisingly quick disappearance, suggests that mepacrine does not act against the unknown causal agent of sarcoidosis but rather against the granuloma cells themselves. The effect, in case 1 at least, seems to have been irreversible. The formation of new sarcoids at a later stage in this patient indicates that the disease has not been cured.

The obvious similarity between the effects of mepacrine and chloroquine in other clinical conditions suggests that chloroquine may be used instead of mepacrine in sarcoidosis. Observations in some other cases of sarcoidosis, now being treated with chloroquine in this clinic, indicate that this may be true, but a definite opinion cannot yet be expressed.

Summary

In two cases of generalised sarcoidosis, treatment with mepacrine resulted in strong brownish discoloration of the cutaneous sarcoids, which were converted into atrophic scars within a month. In both cases other manifestations of sarcoidosis (lymph-node sarcoidosis, sarcoidosis of the nasal mucosa) disappeared together with the cutaneous sarcoids.

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RESECTION OF CARCINOMA OF THE COLON IN THE PRESENCE OF OBSTRUCTION

C. PATRICK SAMES
M.S. Lond., F.R.C.S.

SURGEON TO THE ROYAL UNITED HOSPITAL AND ST. MARTIN'S HOSPITAL, BATH

IMMEDIATE resection of a carcinoma of the left colon in the presence of obstruction is, in selected cases, a justifiable and safe procedure. The principle underlying this procedure is that the growth, with its field of lymphatic spread, is excised; the proximal bowel is brought out as a terminal colostomy; and the distal bowel is closed over and dropped back (rather as in Hartmann's operation for carcinoma of the rectum). At a second operation—which can be postponed for an unlimited time—reconstitution of the bowel is undertaken.

Case-reports

Case 1.—A man of 75 had been investigated as an outpatient and diagnosed as having a carcinoma of the lower pelvic colon. Whilst waiting to come into hospital for operation he gradually became more and more obstructed, and he was finally admitted as an emergency, with absolute constipation for 5 days, which defied treatment with enemata.

At laparotomy a small annular scirrhous growth was found about 3 in. above the peritoneal shelf, without obvious lymph-node metastases and no local fixation. Although the bowel was grossly distended the patient was thin, and radical resection of the growth was undertaken without undue difficulty. The proximal end of the colon was brought out as a terminal colostomy through a gridiron incision in the left iliac fossa, and the distal end was closed with a double layer of sutures and dropped back into the pelvis. 4 weeks later, at a second operation, the colon was reconstituted by dissecting out the colostomy and anastomosing it to the stump of the rectosigmoid.

Case 2.—A married woman, aged 61, presented as an emergency with a history of 5 weeks' generalised colicky abdominal pain and gradually increasing constipation. For the past 3 days she had had virtually no bowel action, and two enemata given the previous day had had no result. She had been vomiting for 24 hours.

At laparotomy, through a left paramedian incision, a carcinoma of the lower pelvic colon was found about 3 in. above the peritoneal shelf. The whole of the large bowel and the terminal ileum was very distended. There were no obvious lymph-nodes or liver metastases. Resection was performed as in the previous case, except that the terminal colostomy was fashioned at the upper end of the abdominal incision. Although the patient was rather obese, no undue difficulty was experienced.

Convalescence was marred by appreciable sepsis of the abdominal wound, with superficial dehiscence of most of its length. This eventually cleared, and the bowel was reconstituted nearly 10 weeks later. At the second operation an incisional hernia was repaired.

Case 3.—A very frail thin lady of 67 was admitted to hospital as an emergency with a diagnosis of "strangulated thrombosed hæmorrhoids", but examination revealed a prolapsed cauliflower-like carcinoma of the colon presenting outside the anus. There was appreciable abdominal distension and visible peristalsis, and absolute constipation of 3 days' duration.

At laparotomy, through a left paramedian incision, the intussuscepted pelvic colon was partially reduced by gentle traction until the head of the intussusceptum, with its associated carcinoma, was felt about 3 in. above the pelvic floor. Attempts at further reduction seemed fraught with danger and were therefore abandoned. There were no obvious liver metastases. Although very distended the patient was extremely thin, and no trouble was experienced in resecting the growth, establishing the colostomy at the upper end of the wound, and closing off the distal stump. Closure of the abdomen was facilitated by aspiration of the colon with a sucker after it had been brought to the exterior but before actual division.

Although it was explained to the patient that the colostomy was not permanent, she seemed so well satisfied that 14 months passed before she could be persuaded to submit to a second operation for colonic reconstitution. This operation went smoothly, and she made an uninterrupted recovery.

Case 4.—A man, aged 61, was admitted to hospital under a physician for investigation of abdominal pain, loss of weight, and diarrhœa. Barium-enema studies showed an obstructive lesion at the rectosigmoid. After the X-rays he became costive and rapidly obstructed, with abdominal distension and vomiting, necessitating emergency surgery.

Laparotomy revealed a carcinoma just above the peritoneal shelf, together with an adherent loop of terminal ileum which was itself obstructive. There were no obvious lymph-nodes or liver metastases. The growth was excised together with a loop of adherent ileum, and enteroanastomosis was performed. The proximal colon was brought out as a colostomy, as in the previous cases. The resection necessitated mobilisation of the rectosigmoid, and the rectal stump was closed below a newly constituted peritoneal shelf.

At a second operation, 9 weeks later, the colon was reconstituted. This proved difficult because ectopic bone had formed in the abdominal wall, and abdominal adhesions were excessive. Great difficulty was also experienced in identifying and mobilising the rectum in the hollow of the sacrum. Because of prolonged ileus convalescence was slow, but the patient eventually made a good recovery, with normal defæcation and continence.

Discussion

For many years surgical teaching has rightly emphasised the dangers of immediate anastomosis of large bowel in the presence of obstruction. The classical procedure involves three separate operations—namely, establishment of a proximal defunctioning colostomy, resection of the diseased segment, and later closure of the colostomy. A

patient presenting with acute intestinal obstruction from carcinoma of the left colon will, therefore, be under surgical care for some considerable time.

Before the antibiotic era the only alternative to this series of operations was the Paul-Mikulicz procedure, where the subsequent closure of the double-barrelled colostomy in an extraperitoneal fashion sometimes reduced the number of stages to two. This was usually not practicable in cases of obstruction, as it did not permit a wide resection of the lymphatic field. With the aid of antibiotics, intraperitoneal suturing has become far safer, but nevertheless immediate anastomosis in the presence of obstruction, and without preliminary bowel preparation, is not to be universally recommended. However, the three-stage operation can now occasionally be reduced to two by simultaneous closure of the colostomy at the same time as the major resection is undertaken. Brooke (1955) advises making a colostomy as near the lesion as is practicable, so that at the second stage both the growth and the colostomy can be resected as one, and the operation can be completed by end-to-end anastomosis.

Until now, except for the Paul-Mikulicz procedure, there has been no satisfactory method of removing the growth at the first surgical intervention. All surgeons have experienced the disappointment of finding that a carcinoma, previously judged operable, has meanwhile become too advanced for curative resection or even for palliation. Often the interval between formation of the colostomy and the second operation is unduly protracted because of postoperative complications, such as wound sepsis or chest complications, or because of administrative errors, such as shortage of beds or operating time, or sometimes delay in acquiescence by the patient. In this way valuable time is lost.

Admittedly occasional cases look inoperable at the earlier inspection, but become more easily resectable when secondary infection and œdema have subsided after colostomy. It must be every surgeon's wish to get the carcinoma away as soon as it is discovered, but with the exception of the Paul-Mikulicz procedure and the somewhat unorthodox method of immediate resection and anastomosis, all other methods involve some delay.

Technical Considerations

Resection of carcinoma of the colon in the presence of obstruction is not to be undertaken lightly, nor by the "occasional" surgeon, and it should be reserved only for selected cases. Handling of the distended coils of bowel is easier where the ileocæcal valve has become incompetent, giving partial decompression of what was formerly a closed-loop obstruction in the colon.

The operation is probably best reserved for cases where the growth is above the peritoneal shelf, for if the rectum is mobilised at the first operation difficulty is found in restoring continuity, as in case 4. The build of the patient is important; in case 3 extreme thinness made the operation exceptionally easy.

Decompression of the bowel by means of a sucker, which is often very disappointing, is probably best performed *outside* the abdomen after the bowel has been brought to the exterior, as contamination is less likely. The temporary colostomy is best sited at the upper end of the paramedian incision, as it facilitates dissection at the second operation. Reconstitution can be deferred indefinitely, and need only be undertaken when the patient's general health is at its optimum.

Summary

A method is described of resecting carcinoma of the colon in the presence of obstruction. Illustrative case-histories are given.

A plea is made for this procedure in selected cases. By this means the growth is removed at the earliest possible time, and the prognosis possibly thereby improved. Also the total duration of illness is shortened.

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PHYSICAL DISORDERS IN PSYCHIATRIC ILLNESS

A STUDY OF 209 CONSECUTIVE ADMISSIONS

C. F. HERRIDGE
M.A., M.B. Cantab.
REGISTRAR TO THE PSYCHIATRIC UNIT, ST. GEORGE'S HOSPITAL, LONDON, S.W.1

IT is well known that a high proportion of patients presenting as general medical or surgical problems, and diagnosed with reasonable confidence as having some organic disease, are eventually found to have no significant physical abnormality. In a recent study, using the Cornell medical index, Culpan et al. (1960) found that of 95 new patients attending the medical outpatient department of a non-teaching hospital, 15% of men and 36% of women were emotionally disturbed; in gynæcological outpatients the figures were even higher—i.e., 52% of 60 new attendances.

Coming from a general medical to a psychiatric unit, I have been impressed by how often the converse is true, and in particular by the number of purely physical conditions initially diagnosed as "functional". Of course, the problem is not an "either or" one; but rather it depends to what extent physical disorders or findings are causal, concomitant, consecutive, or coincidental in psychiatric practice. In 1949 Marshall studied the problem in this unit, and found that no fewer than 44% of 175 patients admitted had some physical state requiring attention. I have made an investigation on similar lines.

The Study

This psychiatric unit has forty-four beds (half male and half female). All patients were seen by one of the medical staff before admission to the unit except for a few transferred direct from other hospitals. Between June, 1959, and February, 1960, inclusive, 209 patients (100 men and 109 women) were admitted. The case-histories and nursing records of this group have been examined, and the principal diagnoses were:

Endogenous depression (including involutional depression)	58
Schizophrenia	35
Reactive depression	22
Hysteria	15
Alcoholism	15
Anxiety state	12
Personality disorder and psychopathy	11
Drug addiction (barbiturates, codeine co., dexamphetamine, pethidine, morphine, carbromal, and trichloroethylene—1 each)	7
Hypomania	7
Toxic confusional states (barbiturates—2, disulfiram ('Antabuse') and bromide—1 each)	4
Arteriosclerotic and senile dementia	4
Hypochondriasis	3
Epileptic sequelæ	2
Neurasthenia, depersonalisation/derealisation, and old general paralysis of the insane (1 each)	3

There was also a group of 11 patients (5%) in whom major physical disease represented the principal diagnosis, but who were referred as having only "functional" illness; these are summarised in table I. It should be

TABLE I—PHYSICAL ILLNESS PRESENTING AS "FUNCTIONAL" SYNDROMES

Case no.	Diagnosis of referring doctor	Final diagnosis
Intracranial disease:		
1	Postinfluenzal depression	Left frontal glioma
2	Loss of sense of time	Right frontal secondary
3	Anxiety from overwork	? Alzheimer's disease
4	Reactive depression to strokes	Left internal-carotid thrombosis
Extracranial disease:		
5	Neurotic reaction to prison sentence	Uræmia. ? cause
6	Involutional depression	Bronchial carcinoma with superior-vena-caval obstruction
7	Hysteria. ? Simmond's cachexia	Tuberculous lung abscess
8	Hysterical reaction to bronchitis	Cor pulmonale and pneumonia
9	Reactive depression after stroke	„ „
10	Post-head-injury defects	Toxic confusion from empyema
11	Senile dementia	Arteriosclerosis and uncontrolled diabetes

noted that in all cases, except nos. 4, 5, 8, and 11, physical illness was diagnosed when the patient was first seen, though often the exact diagnosis was made only after admission to hospital. The term "causal" is applicable to them all. The following case-summaries, which are representative of this group, illustrate how patients' complaints may be misleading unless the situation is further elucidated:

CASE 1.—A 54-year-old hotelier complained of listlessness, lack of interest, inertia, and poor concentration after an attack of "influenza", which had been accompanied by much vomiting, 2 months previously. He admitted to headache only on questioning. He was apathetic and disorientated in time and place, with gross impairment of recent memory. He had papillœdema of the left eye, but no other neurological signs. Ventriculography revealed a large tumour of the left frontal region, and at craniotomy an extensive glioma was removed by frontal lobectomy. Postoperative cerebral œdema developed, and the patient died.

CASE 3.—An optician of 45 complained that his work had got on top of him; he felt depressed, was unable to concentrate, and found difficulty with his accounts. He was superficially well preserved and appeared depressed, but he was slightly dysphasic and showed some lability of mood. He was able to read only slowly and hesitantly, was virtually acalculic, and showed impairment of recent memory. He also had complete finger agnosia, and left-right uncertainty, thus presenting the picture of Gerstmann's syndrome. Ventriculography revealed cerebral atrophy; cortical biopsy was not done.

CASE 5.—A businessman of 47 complained of profuse vomiting, loss of weight, inability to taste, depression, and lack of energy. Investigations by his own doctor had proved negative; and, as he had recently served a prison sentence for income-tax offences which had ruined his career, his illness had been considered psychogenic. He was pale, with a dry scaly skin. For 36 hours after admission he was anuric and he was found to have a blood-urea of 260 mg. per 100 ml., with a secondary anæmia (hæmoglobin 7·4 g. per 100 ml.). His urine contained no protein, he was not hypertensive, and had no retinal changes. With conservative treatment, diuresis started. Renal biopsy was not possible because his blood-urea remained at 200 mg. Hence the diagnosis remains uncertain, though chronic nephritis is most likely.

CASE 6.—A 54-year-old housewife complained of irritability, insomnia, loss of weight, depression and a poor memory, and also of a dry cough and generalised skin irritation. Her social situation was difficult, because her once affluent husband's financial position had declined. Her condition had been investigated in hospital 5 months previously; and, as no physical cause could be found for her illness, she had been referred to a psychiatrist, who had made a diagnosis of involutional depression and given electroconvulsive therapy. She looked depressed and ill, and she had clinical evidence of superior-vena-caval obstruction, with one hard supraclavicular lymph-node. Her memory for recent events was poor, and she showed lability of mood. Chest X-ray revealed a large mass in the anterior mediastinum, and biopsy of the supraclavicular node showed bronchogenic carcinoma. Carotid arteriography showed no evidence of cerebral secondaries. Radiotherapy reduced the size of the mass, and with relief of the caval obstruction her mental state improved.

CASE 7.—A housewife of 26 had complained of headaches and various aches and pains associated with much weight loss, since having a baby 4 years previously. Investigation by her own doctor and an ear, nose, and throat specialist had proved negative, and they thought she was reacting hysterically to a difficult marital situation. She had had mass miniature radiography a year before admission to the unit. Physical examination was negative, but chest radiography revealed a large lung abscess in the left lower lobe. Her sputum teemed with acid-fast and alcohol-fast bacilli. On triple antituberculous therapy she has greatly improved, but may need surgical treatment.

CASE 10.—A slate miner of 44 had sustained a head injury whilst driving under the influence of drink in West Africa. In hospital there, after regaining consciousness 24 hours later, he became progressively disorientated, aggressive, and deluded in a paranoid way. He was flown back to this country with the diagnosis of post-head-injury syndrome. On admission to the unit he was pyrexial and cachectic, and showed a toxic confusional picture. He had a right pleural effusion, and aspiration revealed foul green pus laden with staphylococci. With antibiotics and repeated chest aspiration his physical and mental condition returned to normal.

TABLE II—"CONCOMITANT" PHYSICAL CONDITIONS APPARENTLY CONTRIBUTING TO THE ONSET OF PSYCHOLOGICAL ILLNESS

Physical conditions	No. of patients
Central nervous system: Head injury (3); epilepsy (2); cerebral thrombosis (3); hypertensive encephalopathy; subarachnoid hæmorrhage; general paralysis of the insane; postencephalitic neurasthenia; chemopallidectomy	13
Respiratory system: Influenza (2); pneumonia; asthma	4
Cardiovascular system: Hypertension (2); angina pectoris; cardiac failure; coronary thrombosis	5
Gynæcological conditions (excluding menopause): Puerperium (3); amenorrhœa; dysmenorrhœa; abortion	6
Orthopædic conditions: Prolapsed intervertebral disc; fractured cervical spine; generalised osteoporosis; fractured ankle	4
Oropharynx: Osteomyelitis of jaw; tempero-mandibular arthritis; chronic pharyngitis	3
Arteriosclerosis	3
Alimentary system: Hæmatemesis from gastric ulcer; fissure-in-ano	2
Genitourinary system: Renal and testicular tuberculosis	1
Endocrines: Hypothyroidism	1
Skin: Bromide-sensitivity rash	1
Total	43 (21%)

TABLE III—"CONSECUTIVE" PHYSICAL DISORDERS APPARENTLY RESULTING FROM PSYCHOLOGICAL ILLNESS OR ITS TREATMENT

Physical disorders	No. of patients
Lesions resulting from suicidal attempts (2 before admission)	3
Liver damage from alcohol	3
Pulmonary embolism from deep-vein thrombosis of legs whilst having phenelzine therapy	1
Deep (1) and superficial (1) venous thrombosis of legs whilst having phenelzine therapy	2
Chlorpromazine jaundice	2
Chlorpromazine skin reactions: urticaria (1), maculopapular rash (1)	2
Imipramine skin reaction (urticarial)	1
Liver damage (latent) from iproniazid	1
Total	15 (8%)

TABLE IV—SIGNIFICANT PHYSICAL CONDITIONS APPARENTLY COINCIDENTAL TO PSYCHIATRIC ILLNESS

Physical condition	No. of patients
Respiratory system: ? Active pulmonary tuberculosis (2); chronic bronchitis (3); upper-respiratory-tract infections (4)	9
Alimentary system: Dental conditions (8); peptic-ulcer symptoms (2); hæmorrhoids (2)	12
Cardiovascular system: Symptomless mitral incompetence (1); auricular fibrillation (1); hypertension (2)	4
Orthopædic conditions: Fractured ankle; prolapsed intervertebral disc; fractured jaw	3
Gout	1
Idiopathic hypercholesterolæmia	1
Severe varicose veins and varicose eczema	1
Ophthalmic conditions (excluding errors of refraction)	1
Iron-deficiency anæmia	2
Total	34 (16%)

Of the remaining patients, 69 (34%) were found to have, or developed whilst in hospital, physical illnesses which required attention or further investigation. 18 (9%) of these had multiple physical abnormalities. The physical conditions are detailed in tables II–IV, and the terms concomitant, consecutive, and coincidental may be respectively employed.

Table III shows that 9 patients (4%) developed presumably iatrogenic conditions whilst having modern drug therapy. 3 of these had venous thrombosis of the legs whilst receiving phenelzine, and 1 also had a small pulmonary embolism. None of them was particularly debilitated, or confined to bed, before the thrombosis occurred, though 2 had minor varicose veins. I have not seen another report of this complication of phenelzine therapy.

Discussion

Many patients in whom their own doctors have found no physical abnormality are being referred to the psychiatric outpatient clinics instead of to medical outpatient clinics. Greater vigilance is therefore required on the part of psychiatrists to avoid labelling physical, and potentially treatable, disease as " functional ".

Comroe (1936) was one of the first to become aware of this situation; he found that of 100 patients in a general medical clinic with the diagnosis of neurosis, 24% developed organic disease within 8 months, and in many of these it was present when the original diagnosis was made. Meyer (1958), in a general review of the relation of psychiatry to surgery, has emphasised that because symptoms arise in the midst of an emotional crisis the possibility of organic disease is not excluded. This is further borne out by cases 5, 6, and 7 of the present study, in which a spurious psychogenesis had been attributed to real physical illness. The likelihood of such a mistake will be considerably lessened if one remembers that neurotic reactions are rare in patients of mature years with good previous personalities and no past history of similar episodes.

Cases 1–3, 6, 10, and 11 all showed organic mental syndromes; of these, cases 1, 3, and 6 in particular complained a priori of none of the usual symptoms, but of more nebulous things like depression and listlessness. Organic symptoms should be specifically looked for and inquired after, and the scheme for examination put forward by Mayer-Gross (1954), with particular care in testing for orientation, memory, attention and adaptability, lability of mood, and use of numbers, can be applied simply and quickly in all cases.

A psychiatric opinion is often requested after patients have been " through the mill " in other special departments, and therefore the physical states which may be found are uncommon or atypical. For example, Eilenberg and Scobie (1960) have emphasised the tendency to misinterpret the symptoms of acute porphyria as hysterical.

Finally, the need for a full physical examination of every psychiatric case, irrespective of whether the patient has been referred from another doctor or hospital, is self-evident but often forgotten, as is well illustrated by cases 6 and 10. Furthermore, the full use of all ancillary diagnostic aids is essential. Every patient admitted to this unit has a routine urine examination, chest X-ray, blood-count, erythrocyte-sedimentation rate, and Wassermann reaction. Many important physical conditions would have been missed without.

Summary

The physical disorders amongst 209 psychiatric inpatients have been analysed.

In 5% major physical illness, first discovered on admission to a psychiatric unit, was the principal diagnosis. In 21% physical conditions contributed to the onset of psychiatric illness, in 8% they resulted from it, and in 16% they were unrelated to it.

The dangers of imputing a spurious psychogenesis, and of overlooking organic mental syndromes, must be avoided.

A full physical examination, with radiological and pathological investigation if indicated, is important.

I am grateful to Dr. Desmond Curran, Sir Paul Mallinson, and Dr. Maurice Partridge for permission to study and report on their cases, and to Dr. Curran in particular for much helpful advice and encouragement.

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CYTOMEGALIC INCLUSION DISEASE AND PNEUMOCYSTIS CARINII INFECTION IN AN ADULT

GEORGE WILLIAMS*
M.D. St. And.
SENIOR LECTURER, DEPARTMENT OF PATHOLOGY, MANCHESTER UNIVERSITY

T. B. STRETTON
M.B. Manc., M.R.C.P.
MEDICAL REGISTRAR, ROYAL INFIRMARY, MANCHESTER

J. C. LEONARD
M.D. Lond., M.R.C.P.
SENIOR REGISTRAR IN MEDICINE, ROYAL INFIRMARY, MANCHESTER

CYTOMEGALIC inclusion disease is a viral infection which has been recognised in infants for some years (Farber and Wolbach 1932, Wyatt et al. 1950, Seifert 1954, Nelson and Wyatt 1959). It may be localised to the salivary glands, when it is usually found incidentally at necropsy, or it may be a severe, sometimes fatal, generalised illness (Worth and Howard 1950). In adults, cytomegalic inclusion disease is rare and takes a different form. It may be confined to a single organ in association with other diseases, notably those of the reticuloendothelial system (Hamperl 1956). In a more generalised form, it is often accompanied by other systemic diseases (Fisher and Davis 1958).

Pneumocystis carinii is thought to be a protozoon and was first alleged to be responsible for interstitial plasma-cell pneumonia of infants by Vaněk and Jírovec (1952).

* Present address: University of Vermont College of Medicine, Burlington, Vermont, U.S.A.

This disease was initially recognised in central Europe (Rossle 1923, 1928, Ammich 1938). Later, cases were reported from Scandinavia (Linell 1949, Gormsen 1950), Great Britain (Baar 1955), North America (Lunseth et al. 1955), and Australia (Reye and ten Seldam 1956). An association between this condition and cytomegalic inclusion disease has been observed in infants (Dittrich and Seifert 1953, Baar 1955, Berdnikoff 1959). This form of combined infection appears to be extremely rare in adults (Hamperl 1956, Symmers 1960).

Clinical Report

A man, aged 25, was admitted in April, 1959. For two years he had had chronic gingivitis which improved temporarily after gingivectomy in November, 1958. Throughout 1958, he had had variable non-irritant lesions on the skin of his back and shoulders. He attended elsewhere for dermatological advice during this time; the diagnoses included neurodermatitis, eczema, and tinea; and he was treated with X rays, local hydrocortisone (1% cream), and chlortetracycline (1% cream).

His general health was good until December, 1958; he then gradually developed breathlessness on exertion, nocturnal sweats, anorexia, loss of weight, tiredness, and fever. He had a cough, producing mucopurulent sputum with a few scanty hæmoptyses. He had had slight pruritus ani for some years, and had hæmorrhoids which bled occasionally. In February, 1959, a painful, indolent anal fissure developed, and gradually extended backwards and forwards from the anal margin. This enlarging ulcer had a shallow edge and a deep centre. In April, 1959, a small papule appeared in one nostril. The papule ulcerated and slowly increased in size.

He was wasted, febrile, and ill. There was moderate generalised gingivitis. A few scaly brownish lesions were seen on the skin of his back and shoulders. There was no enlargement of lymph-nodes, and no abnormalities were found in the cardiovascular system (blood-pressure 120/75 mm. Hg), lungs, abdomen, or central nervous system. The anal ulcer extended 3 in. in the natal cleft behind the anus and 1 in. anteriorly; it was covered by a purulent exudate. A small papule was seen at the tip of the left nostril.

Investigations

The hæmoglobin ranged from 94 to 108% (13·9–16·0 g. per 100 ml.) and the white-cell count from 7300 to 10,800 per c.mm. (the differential count was normal). His erythrocyte-sedimentation rate was also normal (2 to 8 mm. in the first hour) except during an attack of bacterial pneumonia when it rose to 30 mm. The serum-albumin was between 3·3 and 4·5 g. per 100 ml., falling to 2·1 g. on Aug. 20, 1959. The serum-globulin was between 2·3 and 2·4 g. per 100 ml.

Serial chest radiographs showed fine nodular opacities throughout both lungs, with partial clearing after the administration of steroid drugs. The sputum was examined many times; acid-fast bacilli were not seen and all cultures for *Mycobacterium tuberculosis* were negative. The Mantoux test was negative at a strength of 1/10. The fæces contained no pathogenic organisms, and swabs from the anal fissure showed debris and gram-negative bacilli; culture produced a growth of *Bacillus proteus* and a coliform organism. Blood-cultures were repeatedly sterile. The Wassermann reaction and the Kveim test were both negative. Examination of the sternal marrow showed a nucleated-cell count of 178,000 per c.mm. There was generalised hyperplasia of all normal elements and plasma cells were present. Tissue was taken for microscopic examination from the anal and nasal lesions, and a scalene node was also removed. The anal lesion consisted of a non-specific granulomatous ulcer; the nasal lesion was ulcerated, granulomatous, and densely infiltrated with polymorphonuclear leucocytes and lymphocytes; there were no eosinophils or vascular damage. The scalene node showed some reactive hyperplasia but was otherwise normal.

Progress and Treatment

An initial diagnosis of miliary tuberculosis was made in view of his high fever, severe constitutional symptoms, and the radiological findings. He was treated with streptomycin 1 g. daily, isoniazid 100 mg. twice daily, and *p*-aminosalicylate 6 g. twice daily for twelve weeks. There was no response to treatment and, because of the negative reaction to tuberculin, the diagnosis was abandoned. Other diagnoses which were considered included sarcoidosis, the reticuloses, and Wegener's granulomatosis. After two months, prednisone 10 mg. three times daily was added to the antituberculous regimen. This produced a temporary improvement in his symptoms; the pyrexia subsided for several weeks, his appetite improved, and he gained weight. The anal lesion, however, had progressed remorselessly to involve a wide area of his buttocks, extending several inches on each side of the natal cleft (fig. 1a). The nasal lesion broke down into a chronic ulcer which eroded the nasal cartilages and spread to the lip (fig. 1b). An indolent paronychia of the left index finger developed. In the last month of life, fresh ulcers appeared on the dorsum of the tongue and the lower lip. Local radiotherapy was given to the ulcerated areas, but without any convincing benefit. Three weeks before

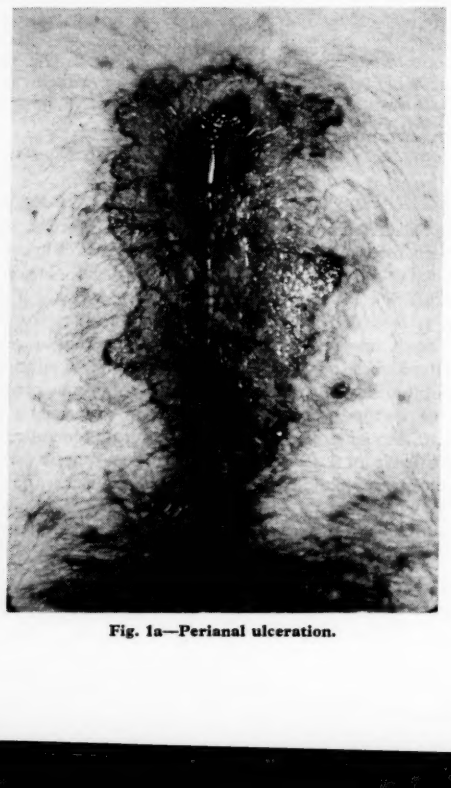

Fig. 1a—Perianal ulceration.

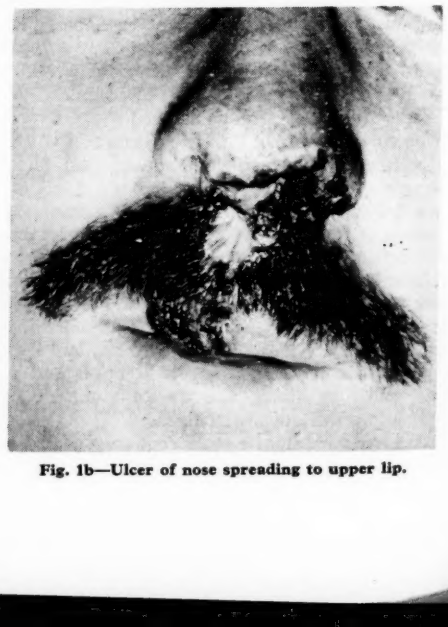

Fig. 1b—Ulcer of nose spreading to upper lip.

death he had severe bronchopneumonia which partially responded to treatment with erythromycin 500 mg. six-hourly, and chloramphenicol 500 mg. six-hourly for ten days; but he steadily became weaker, dying some four and a half months after admission. Latterly there was central cyanosis with increasing tachypnœa and early clubbing of the fingers.

Postmortem Appearances

External

The body was severely emaciated. The epidermis lying between the nasolabial folds was largely desquamated from an underlying smooth, moist dermal surface. The perianal ulcer, its base covered by serofibrinous exudate, extended over the buttocks with an ill-defined, undermined edge. The nasal and finger lesions were similar, though smaller. Numerous small lesions, some pustular, others dry and encrusted, were distributed irregularly over the skin of the thorax, abdominal wall, scapular regions, and inner aspects of thighs.

Internal

The lining membranes of the nose, mouth, pharynx, and larynx were ulcerated and covered with purulent exudate; ulcerated plaques were present on the dorsum and lateral margins of the tongue. The trachea was congested and contained a little mucopus, but was not ulcerated.

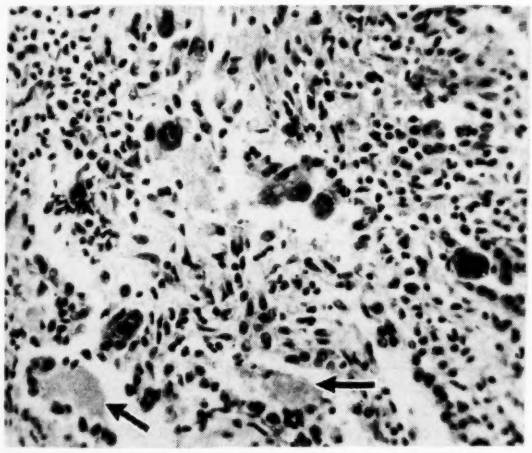

Fig. 2—Lung showing interstitial pneumonia and cytomegaly with inclusions. Aggregates of pneumocystis lie in alveoli (arrows). (Hæmatoxylin and eosin. ×230.)

Lungs.—In the right lung (weight 485 g.): the lower lobe was partially collapsed; there was extensive fibrinous exudate over the diaphragmatic and lateral pleural surfaces associated with an empyema (about 250 ml.) from which coagulase-positive *Staphylococcus aureus* was later cultured. Section of the lung showed a uniform grey-white consolidation of all lobes with a hæmorrhagic zone adjacent to the empyema. Bronchi at the base contained small quantities of mucopus; the remaining bronchi contained mucoid material only. The pulmonary arterial tree was normal.

The left lung (weight 480 g.) was of firm consistence; its cut surface showed extensive areas of grey-white consolidation sharply defined from limited areas of aerated tissue. Small quantities of mucoid material were present, mainly in the bronchi of the lower lobe. The main pulmonary arteries appeared normal. The hilar and mediastinal lymph-nodes were moderately enlarged and rather fleshy, with foci of carbon pigmentation.

Other organs.—The pericardial sac contained approximately 7 ml. of brown-stained fluid and showed a slight fibrinous exudate over the apex.

The spleen (210 g.) was moderately enlarged and soft. The liver (1950 g.) was enlarged and rather flabby, with a pale cut surface, showing occasional hæmorrhagic foci. The lobular pattern was maintained.

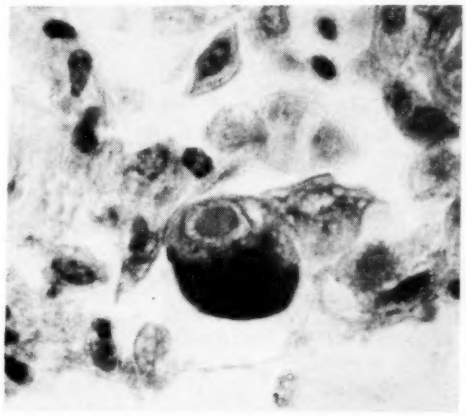

Fig. 3—Lung. Cytomegalic inclusion cell showing typical intranuclear and intracytoplasmic inclusions. (Giemsa. ×700.)

The only lesion seen in serial sections of the brain was a solitary, pale brown, circumscribed focus 0·5 cm. in diameter situated in the cortical grey matter of the left parietal lobe.

Histological Examinations

The lungs showed a fairly generalised, bilateral interstitial pneumonia. The alveolar septa were thickened and infiltrated, mainly by small lymphocytes and, to a lesser extent, by plasma-cells. The alveolar lining epithelium was cubical in many areas and frequently shed into the alveolar lumina which contained numerous lipid-laden phagocytes. Large cells, typical of cytomegalic inclusion disease, were present in all lung fields, being particularly striking in some areas (fig. 2). The intranuclear inclusions were strongly basophilic; they stained red or red-brown in phloxine-tartrazine preparations and blue with Mallory's phosphotungstic-acid/hæmatoxylin. Between the intranuclear inclusion masses and the nuclear membrane, which often showed margination of nuclear chromatin, there was in most instances a clear halo. Within the cytoplasm there were clusters of small inclusions, shown well in Giemsa preparations as small blue bodies (fig. 3). Scattered irregularly throughout the lungs, sometimes densely, were honeycomb masses of light-refracting bodies, characteristic of the cysts of *Pneumocystis carinii*. These masses reacted strongly to periodic-acid/Schiff and to the methenamine silver stain of Gomori, and with a lesser intensity, to the Weigert-Gram (fig. 4) and Gridley stains (1953). Some of the cysts contained four or eight distinct spores; others

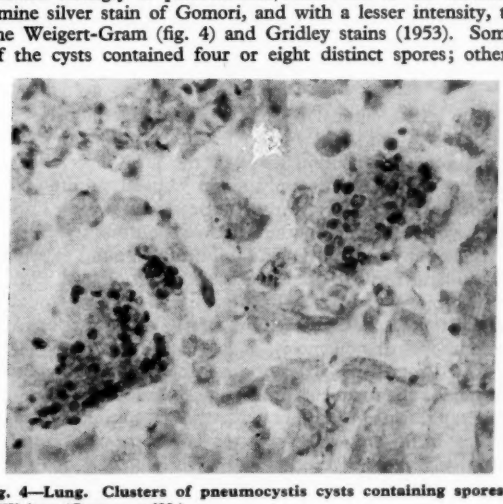

Fig. 4—Lung. Clusters of pneumocystis cysts containing spores. (Weigert/Gram. ×480.)

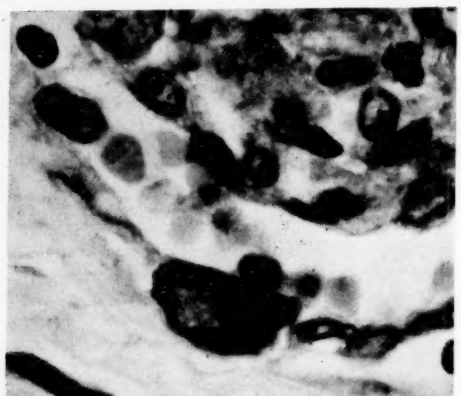

Fig. 5—Skin lesions. Capillary in granulation tissue showing inclusions in nuclei and cytoplasm of endothelial cell. (H. & E. ×870.)

appeared degenerate and void of spores. Occasional spores or spore-bearing cysts were located with the alveolar septa.

The Skin Lesions

The lesions around the mouth and in the perianal region were non-specific granulomatous ulcers. Secondary infection contributed to most of the lesions in the mouth or pharynx. A careful search failed to show evidence of parasitic and fungal infection in these sites. In the circumoral and perianal lesions, and in the ulcerated plaques on the tongue, intranuclear inclusions were found in some of the cells (presumably endothelial) lining, or in close relation to, the lumina of the capillaries of the granulation tissue (fig. 5).

Elsewhere, the smaller skin lesions consisted of encrusted, non-specific superficial ulcers, or small intradermal abscesses. Occasional small, herpetiform vesicles occurred in the hypertrophic squamous epithelium of the tongue.

The cellular focus of the brain lesion consisted of astrocytic cells with granular nuclei, oligodendrocytes, microglial cells, and a few surviving neurones in a rather vascular stroma. Search for both inclusion bodies and protozoa proved negative, although unusual amounts of extracellular granular material positive to periodic-acid/Schiff were present. The nature of this lesion is uncertain; the histological appearances suggest either an early astrocytoma, though in an unusual site, or alternatively a hamartomatous glial nodule.

Discussion

The initial clinical diagnoses were tuberculosis or a reticulosis. The outstanding features at this time were the severe constitutional symptoms and fever, out of keeping with the relatively slight clinical findings; the major lesion was the already advanced anal ulcer. Tuberculosis was excluded by the negative Mantoux test, failure to isolate any organisms, and failure to respond to appropriate treatment. A reticulosis seemed unlikely in view of the biopsy reports. Sarcoidosis was considered but later progress and the results of the investigations did not support this diagnosis.

The progressive extension of the nasal ulcer finally suggested the diagnosis of Wegener's granulomatosis; the general features, together with the ulceration, appeared typical of this condition (Walton 1958), though there was no involvement of the kidneys. Anal ulceration, as seen in our patient, does not appear to have been described, though the case of Short (1957) had shallow necrotic ulcers over the buttocks. Wegener's granulomatosis was the presumptive clinical diagnosis at the time of death.

From the pathological point of view, the main interest lay in the lung and skin lesions. Histologically there was no evidence of Wegener's granulomatosis. The main pulmonary lesion was a severe interstitial pneumonia associated with cytomegalic inclusion disease and a patchy pneumocystis infection. The patchiness of this infection and the pulmonary macrophage response indicated some degree of resistance on the part of the host, whose death was finally hastened by a terminal staphylococcal pneumonia and empyema. This is in contrast to the overwhelming pulmonary protozoal infections encountered in the majority of infants suffering from pneumocystosis.

The possibility of Behçet's disease was rejected because of the distribution and progressive nature of the skin lesions, together with absence of eye and joint symptoms, and central nervous system lesions (France et al. 1951, Curth 1952). The only specific features of the lesions in the skin were the presence of intranuclear and intracytoplasmic inclusions in the endothelial cells of related capillaries. These are an accepted feature of cytomegalic inclusion disease in its generalised form (Symmers 1960). Hartz and van de Stadt (1943) described similar inclusions in the capillaries in a biopsy specimen from a pedunculated anal tumour in a 35-year old coloured woman.

Generalised cytomegalic inclusion disease in the adult has been described in association with toxoplasmosis and myeloid metaplasia (Hemsath and Pinkerton 1956), myeloid leukæmia (Fisher and Davis 1958), and with *Pneumocystis carinii* infection and severe systemic diseases (Symmers 1960). In our case, if one accepts the staphylococcal lung infection as a terminal event, no severe underlying disease was found, the small brain lesion being regarded as fortuitous. Although agammaglobulinæmia or hypogammaglobulinæmia could not be excluded on the data available, the normal total serum-protein levels and abundance of plasma-cells in the bone-marrow and tissues make this unlikely. Steroid therapy, however, probably contributed to a decreased host resistance in this case, thus encouraging extension of the infections, and possibly allowing these saprophytic organisms to adopt a pathogenic role. This possibility has been demonstrated with a wide variety of bacteria, viruses, protozoa, and fungi (Kass and Finland 1953).

The pattern of generalised cytomegalic inclusion disease may vary, but the lungs, adrenals, liver, spleen, and kidneys are most commonly involved. Lesions varying from early degenerative changes to frank cellular necrosis have been described in these organs. The view advanced by von Glahn and Pappenheimer (1925) that this is a viral disease has been confirmed by the recent experimental work of Smith (1956) which also supported the probable species-specificity of the virus. Nor is the virus purely epitheliotrophic—for example, Vogel (1958) found specific inclusions in fibroblasts, heart-muscle cells, and mesothelial and endothelial cells, in a 10-year-old boy dying from the disease. He also successfully reproduced comparable endothelial inclusions in the capillaries of experimental granulomata in mice inoculated with mouse inclusion virus.

The association with *Pneumocystis carinii* infection was of further interest. This form of alleged protozoal infection has now become an established pædiatric hazard with a predilection for premature, debilitated, or

congenitally afflicted infants (Vaněk and Jírovec 1952, Hamperl 1952, Herzberg et al. 1952), but it has very rarely been found in adults. Isolated adult cases have been reported, associated with other concurrent diseases (Meer and Brug 1942 Jírovec and Vaněk 1955), whilst Hamperl (1956) demonstrated the infection in a case of fatal inclusion pneumonitis reported by McMillan (1947) and suggested the probability in two similar cases of Wyatt et al. (1953). Simultaneous pneumocystis and cytomegalic inclusion infections have also been described by Berdnikoff (1959) in an infant. The association of these two apparently separate and normally saprophytic infections is interesting, and perhaps not entirely fortuitous, especially since the nature of the pneumocystis organism has not yet been determined. In due course a closer relationship may be established. It is important to recognise their potential pathogenicity and their ability to produce, either alone or in combination, fatal infections in man.

There is some evidence that this danger is increased by prolonged treatment with steroids and antibiotics (Symmers 1960). Possibly more cases will occur because of the increasing use of these drugs. At present, there is no effective treatment.

Summary

A fatal case of combined cytomegalic inclusion disease and *Pneumocystis carinii* infection is described in a man aged 25. The main clinical features were a long-continued and progressive oronasal and perianal ulceration with severe constitutional disturbance, followed by increasing pulmonary distress ending in bronchopneumonia and empyema.

At necropsy, the main lesions were restricted to the lungs and skin; they included extensive grey-white consolidation of both lungs associated with staphylococcal empyema, severe ulceration in and around the mouth and in the perianal region, together with more generalised ulceration of the skin. Histologically the pulmonary lesion proved to be a severe interstitial pneumonia associated with cytomegalic inclusion disease and *Pneumocystis carinii* infection. The skin lesions were explicable in terms of giant-cell inclusion disease.

Very rarely both infections described have been found together in adults in association with serious underlying diseases; no underlying disease was identified in this patient. The nature of the infections is discussed and reference is made to the risk of converting these saprophytes into pathogenic organisms by prolonged treatment with steroid drugs and antibiotics.

We are grateful to Dr. C. S. D. Don for permission to publish this case; to Prof. A. C. P. Campbell and Prof. H. Hamperl (Bonn) for help in preparation; and to Mr. N. Mowat and Mr. G. Saville for technical assistance.

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PSEUDOTUMOUR OF THE ORBIT AND WEGENER'S GRANULOMA

J. STEVEN FAULDS
M.D. Edin., F.R.F.P.S.
PATHOLOGIST

A. ROSS WEAR
M.B. Leeds, D.O.
OPHTHALMIC SURGEON

CUMBERLAND INFIRMARY, CARLISLE

THE clinical condition known as "pseudotumour of the orbit" is a well-recognised, though relatively rare, lesion. Its cause is unknown, but recent work suggests that it belongs to the group of diseases which show chronic inflammatory reaction to a non-bacterial agent. This group includes polyarteritis and Wegener's granuloma (Walton 1956a and b, 1958). Duke-Elder (1952) describes orbital pseudotumours as "cases which are difficult to differentiate clinically from an orbital tumour, but which, on pathological investigation or by their resolution under treatment, are shown to be granulomata of chronic inflammatory origin".

Our case was diagnosed clinically and histologically as pseudotumour of the orbit. At necropsy the condition was found to be Wegener's granuloma, an ulcerative, granulomatous lesion primarily involving the respiratory tract; and, in this case, with secondary involvement of the orbital tissue from the nasal sinuses.

Several fatal cases of Wegener's granuloma of the mouth and nose have been seen in Cumberland during the past thirty years, three of which were published by Walton (1956b), who subdivides the condition into three types: (1) associated with polyarteritis; (2) typical malignant granuloma usually involving the upper respiratory tract, and, though not histologically malignant, invariably fatal; and (3) granuloma gangrænescus—a histologically malignant sarcomatous lesion associated with extensive local destruction.

In our patient a granulomatous lesion, initially involving the orbit and ethmoidal sinus, eventually spread to the skull bones and cranial cavity. Later the lungs became involved, with cavitation and a purulent sputum. The disease progressed steadily, and proved fatal in two years. At postmortem examination, polyarteritis was found, with ischæmic necrosis and scarring of the kidneys.

Case-record

A woman, aged 35, was first seen in June, 1956, when she complained of diplopia and orbital pain of four weeks' duration. The left eye was found to be proptosed and a firm swelling, painless on pressure, was palpable under the lower lid, attached to the medial margin of the orbit, pushing the eye upwards and outwards. Both eyes were healthy, and vision was 6/6

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in each; the left lacrimal duct was freely patent, and an X-ray showed an opaque left maxillary sinus but no erosion of the bone. The aural surgeon's opinion was that the nasal cavity was not the cause of the infection, though crowding of the left olfactory cleft was observed, with crusts which bled easily. He considered that the sinus was being involved secondarily to the orbit. The sinus was punctured and washings contained purulent material, mainly necrotic tissue infiltrated by polymorphonuclear leucocytes and round cells. No malignant cells could be seen, and no organisms grew on culture. Conjunctival swabs were sterile; Wassermann and Kahn reactions negative; X-rays of chest and skull normal; and the Mantoux test negative at a dilution of 1/1000.

At operation on Aug. 16, 1956, a large solid non-encapsulated mass was found occupying the lower part of the orbit and infiltrating the inferior rectus and orbicularis muscles. A good part of it was removed, but a flat extension went back to the apex of the orbital cavity and was inaccessible. The histological report on this material stated that it was mostly fibrous tissue with numerous centres of inflammation, infiltrated with plasma-cells and polymorphs and with one or two "atypical giant cells". There was no evidence of sarcoidosis, tuberculosis, or tumour, nor could any organisms be demonstrated in the sections. A section was sent to the Institute of Ophthalmology in London, where it was reported to be a "non-specific granuloma of orbit, commonly known as a pseudotumour of the orbit, the ætiology of which is obscure".

After a temporary improvement, the proptosis recurred and on Dec. 4, 1956, the patient was referred to the neurosurgical unit in Newcastle, with increasing ptosis, ophthalmoplegia, papillœdema, and detachment of the retina. On Dec. 19 an orbital decompression was carried out, the roof and lateral wall of the orbit being removed; part of the tumour was excised. It was reported to be histologically "chronic granulation tissue".

Fig. 1—Lung with large abscess cavity in lower lobe.

Her sight improved after this operation; but ten months later the mass had enlarged, and, by pressure on the eye, caused acute glaucoma. The eye was removed and the orbit exenterated. A section was sent to the Institute of Ophthalmology and again it was reported to be a "pseudotumour of the orbit". The patient now developed bilateral inner-ear deafness which became extreme. An increase in the size of the thyroid gland was observed, and this was confirmed by the increased absorption of radioactive ^{131}I, but there was no other evidence of hyperthyroidism. The pain in the left orbit and left side of the face was increasing and was not controlled by simple analgesics. In December, 1957, she was treated with deep X-ray therapy, antibiotics, and prednisone, without much response. After this she developed severe anæmia and became totally deaf. In January, 1958, a further intensive course of high-voltage X rays, combined with erythromycin, was given, because the condition was considered to be a malignant granuloma of the upper respiratory tract. Considerable regression of the tumour mass resulted, with alleviation of the pain.

By April, 1958, the patient had enlarged submaxillary lymph-nodes, severe anæmia, and sloughing of the left upper lid. The orbital cavity was filled with granulations. Proptosis of the right eye and enlargement of the right pre-auricular lymph-node developed. A hard mass was palpable below the angle of the right mandible. There was abundant purulent sputum and further therapy was considered useless. She died at home on May 23, 1958.

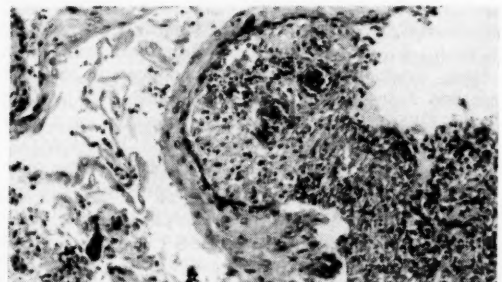

Fig. 2—Squamous epithelial lining of lung abscess, with "eosinophilic" protein deposit among cells. (×100.)

Postmortem Findings

A large ulcerated area occupied the left orbit, which was completely destroyed and replaced by a putrefying abscess cavity. This communicated with the ethmoid sinuses and extended into the cranial cavity over the inferior surface of the left frontal lobe. There was no evidence of meningitis, or of infection or abnormality in the brain.

Respiratory tract.—There was no abnormality in the mouth or pharynx, but unfortunately the nose and sinuses were not examined in detail as the clinical notes were not available at the time of the postmortem examination. The trachea and bronchi were filled with purulent sputum. The right lung had a large, irregular, abscess cavity, 9×6 cm., in the lower lobe, lined by shaggy purulent granulations and containing foul-smelling pus (fig. 1). The remainder of the lungs showed a diffuse bronchopneumonia and purulent bronchitis, but there were no other cavities and there was no evidence of tuberculosis. Microscopically, the abscess cavity was mostly lined by pyogenic granulations containing deeply stained giant cells. Areas of the abscess cavity were lined by squamous epithelium, and between certain of the cells were collections of pink-stained protein deposit similar to that seen in the capillary loops in periarteritis (fig. 2). No histological evidence of tuberculosis or tumour was found.

Fig. 3—Kidney with depressed white scars caused by fibrosed areas.

Cardiovascular system.—There was no cardiac enlargement, arteriosclerosis, or evidence of hypertension.

Urinary system.—Both kidneys were irregular in shape, and through the capsule could be seen many pale areas suggestive of secondary

tumour (fig. 3). The capsule stripped easily, revealing multiple depressed scars approximately 1 cm. in diameter. On section, the pale areas were found to be wedge-shaped, with the apex pointing to the medulla. From the naked-eye appearance, they were considered to be the result of ischæmic necrosis from endarteritis. Microscopically these areas resembled the original tissue taken from the orbit. The renal tissue was necrotic and could be recognised as an indifferently stained material in which shadows of glomeruli, tubules, and vessels were visible. At the edge of the "infarcted" area, proliferating fibroblasts, along with lymphocytes and atypical giant cells, were present, and the glomeruli had a thickened capsule with the capillary loop obstructed by eosinophilic material. A number of the glomeruli were fibrosed and surrounded by fibrous tissue (fig. 4). The initial lesion appeared to be a glomerulitis with primary involvement of the capillary loop, but an explanation for the wedge-shaped necrotic zones could not be found, as there was no thickening or obstruction of the larger arteries or arterioles (fig. 5).

Discussion

Both diseases—Wegener's granulomata and pseudotumour of the orbit—have been described in recent well-documented reports, but, so far as we know, recognition of the two conditions in the one patient has not been recorded. Orbital involvement occurred in several of the

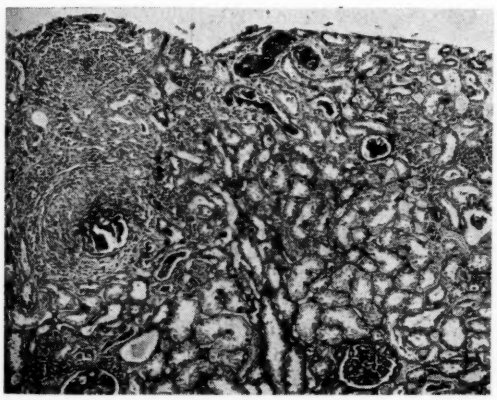

Fig. 4—Kidney: fibrosed area. (×100.)

cases quoted by Walton (1959a) which were not considered clinically as cases of pseudotumour, and Jackson (1958) likewise noted the frequency of involvement of the nasal side of the orbit, suggesting an association with the nasal sinuses and cavity. Jackson also observed an association of eye lesions with a granulomatous lesion in the lung and considered pseudotumour to be a specific disease primarily related to the air-passages, but did not link it up with Wegener's granulomatosis.

In our case, the presenting symptom was the lesion in the left eye, and at an early stage an abnormality was observed in the corresponding side of the nose, which was considered to be secondary to the orbital lesion. In spite of the obvious pulmonary lesion, the failure to respond to treatment, and the involvement of the ears (a feature recorded in many cases of Wegener's syndrome), the correct diagnosis was not suggested until just before death.

The postmortem renal findings of glomerulitis, arteritis, and the multiple scars caused by the wedge-shaped granulomatous fibrosis, along with the pulmonary changes, is characteristic of a Wegener's granuloma. An arteritis was observed in the spleen and pulmonary vessels as well as in the kidneys, and a peculiar eosinophilic protein

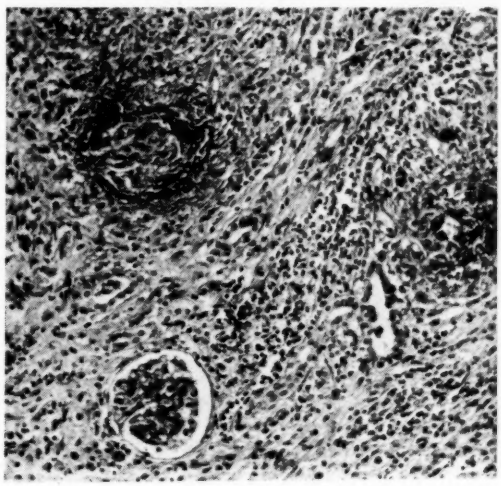

Fig. 5—Kidney: fibrosed glomerulus. (×100.)

material was found between the squamous epithelial cells lining the large abscess cavity in the lung. This material resembled that found in systemic lupus erythematosus. The similarity of the renal changes found in both Wegener's granuloma and lupus erythematosus has been noted by many. In Walton's case of pseudotumour with polyarteritis (1959b), renal infarcts were shown but no granulomatous changes were seen, and only a few of the glomeruli showed fibrinoid changes in the capillaries.

The cause of both conditions is unknown. No infective agent has been isolated, and, though Symmers (1960) demonstrated *Pneumocystis carinii* and cytomegalic inclusion bodies in his case, he concluded that they were the result and not the cause of the trouble. A widely held view is that Wegener's granuloma and pseudotumour are iatrogenic diseases produced by the administration of antibiotics and sulphonamides. This can be discounted because both conditions were recognised before either therapeutic agent had been invented. A sensitivity to drugs has been observed in our case, as in most others. For that reason, antibiotics, particularly streptomycin and the sulphonamides, are often blamed for aggravating both lesions and are never found to help.

From relevant publications and the appearances in this case we consider that pseudotumour is an orbital manifestation of Wegener's granuloma and that both conditions are specific tissue reactions to an agent not so far identified.

Summary

A case is presented of pseudotumour of the orbit and coexistent Wegener's granuloma, and it is suggested that the two conditions are linked ætiologically.

We are indebted to Dr. A. C. Ogilvie, who carried out the post-mortem examination at Workington Infirmary, for a copy of his notes and for giving us the specimens to study; to Mr. G. F. Rowbotham, of the neurosurgical unit, Royal Victoria Infirmary, Newcastle, for the use of his notes; and to Prof. J. B. Duguid, Newcastle, who helped to solve the problem.

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Preliminary Communications

INFRA-RED RADIATION THERMOMETRY IN CLINICAL PRACTICE

WHILE we were trying to devise a method of locating incompetent perforating veins in patients with varicose veins, it occurred to one of us (K. Ll. W.) that the skin temperature might be greater at the point where a perforating vein " surfaced ", and that infra-red emission from the skin would, therefore, be increased. This idea, though not so far very successful in application, proved a starting-point for a more general consideration of infra-red emission from the skin under normal conditions and in pathological states.

It has long been known that skin (whether white or pigmented) behaves as a black-body radiator [1–4] and that infra-red emission from it therefore bears a direct relationship to the surface temperature.[5] The measurement of skin temperature from infra-red radiation has great advantages over direct thermometry (e.g., by thermocouples) because (1) the rays can be measured at a distance and contact with the skin is unnecessary, (2) it is very rapid, and (3) measurement at a distance yields an average reading for a small area of skin rather than for a point, and this tends to compensate for local variations in capillary tone.

Infra-red waves emitted from the skin have a wavelength varying from 4 to 20μ, with a peak emission at 9μ, and highly sensitive instruments are available for measuring them. It was decided that a Schwarz thermopile, fitted with calcium-fluoride window, transmitting wavelengths up to 11μ, was the most suitable detector available. Measurements were made at a distance of 1 cm. from the skin, the current produced by the thermopile being measured by deflection of a mirror galvanometer. A contact thermocouple was used to verify the direct relationship between the infra-red emission and the surface temperature. The deflection per degree centigrade was determined by comparison with the radiation from the blackened face of a Leslie cube at known temperature.

CLINICAL APPLICATION

When clinical observations of infra-red radiation from the skin were to be made, the patient was unclothed and left in a room of constant known temperature for ten minutes. Readings were then taken with the thermopile at 1 cm. distant from the skin over the area of pathological signs, immediately followed by readings made on the same area of the other (normal) side of the body. Our early observations were made over swellings which were obviously hot to touch and we were astonished to find that the skin temperature over a superficial abscess might be raised by as much as 5°C above the normal area on the other side. On several occasions, temperatures 1°C or more above the rectal temperature were recorded. An abscess in the rectus sheath was demarcated by scanning it with the thermopile, and it was also found that regional lymph-nodes, enlarged by inflammation, were hotter than those on the contralateral part of the body.

A series of breast swellings was next investigated. The findings in this series are being reported more fully elsewhere. 32 out of 34 carcinomata were hot as compared with the same area in the other breast—an observation already made by Lawson.[6 7] The temperature difference was often of the order of 2–3°C, and was measurable by relatively crude instruments.

The rise in temperature over malignant tumours was not confined to breast cancers, but occurred over other superficial tumours. Amongst those investigated were secondary deposits in the breast from carcinoma of the bronchus, secondary deposits in the neck from hypernephroma, metastatic nodules in distant sites from a primary site in the breast, malignant melanomata, superficial deposits in lymphosarcoma and Hodgkin's disease, fibrosarcomata of the calf and pectoralis major muscle, carcinomata of the parotid, and secondary deposits from carcinoma of the breast and malignant melanomata in superficial lymph-nodes. In all these cases there was an increased emission of infra-red rays over the swelling as compared with the surrounding skin and the normal side. Some benign fibroadenomata of the breast were also " hot ", and in a few cases were indistinguishable thermometrically from carcinomata; the " hot " fibroadenomata appeared to be of the softer and more rapidly growing variety. Benign nævi of the skin and one sclerosing hæmangioma were, however, of normal temperature. Fibrosis, adenosis, and cysts in the breast were either of normal temperature, or occasionally, in the case of cysts, were actually 1 to 2 degrees colder than the surrounding skin and the other side. There was only one exception where a cyst was " hotter ", and subsequent histological examination showed this cyst to be acutely inflamed.

Skin temperatures in patients with peripheral vascular disease have also been measured by this method, and a drop in temperature over the site of a localised vascular occlusion in a limb has been observed. In two cases the estimated site of the block has been confirmed by arteriography, and in two cases a below-knee amputation has been performed successfully for arteriosclerosis where the below-knee temperature appeared to demonstrate an adequate blood supply. It has also been used as a rapid method of temperature measurement in assessing the effect of lumbar sympathetic block. It is possible to demonstrate the site of incompetent perforating veins in varicose ulceration by means of a rise in temperature at the spot where deep venous blood is forced to the surface by the calf pump, but the method of demonstration is at present too tedious to be of clinical value. It has also been observed that some varicose ulcers are hot and others cold. Hæmangiomata and arteriovenous fistulæ also exhibit a raised temperature.

Finally, in a small series of cases, observations have been made of the changes in temperature of superficial carcinomata during and after radiotherapy and chemotherapy.

DISCUSSION

Although it must be emphasised that observations have hitherto been made on only a small number of cases, the results have been so uniform that the method seems to deserve further investigation. It is clear that subcutaneous inflammatory processes and rapidly growing neoplasms, whether innocent or malignant, increase infra-red radiation from the overlying skin. In an organ such as the breast, which is subcutaneous and in which distinction of degenerative from neoplastic swellings may be difficult,

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5. Bohnenkamp, H., Ernst, H. W. *Pflug. Arch. ges. Physiol.* 1931, **228**, 63.
6. Lawson, R. N. *Canad. med. ass. J.* 1956, **75**, 309.
7. Lawson, R. N. *Canad. med. Serv. J.* 1957, **13**, 517.

measurements of infra-red radiation may give considerable help in diagnosis. It may also prove to be useful in determining gross increases or decreases in blood-supply due to vascular disease, and, in particular, may give a rapid, simple and safe method of determining the level of amputation in an ischæmic limb.

At first sight, it might be supposed that infra-red thermometry was tantamount to measuring increases and decreases in blood-flow. It is difficult, however, to explain in terms of vascularity alone why, in several examples of inflammation and neoplasm, skin temperatures over the lumps were found to be higher than the rectal temperatures by as much as 1·5°C. A rise of temperature in an area of skin caused solely by increased transference of heat to that area by the blood-stream could not surpass that of the interior of the body. Nor would a purely vascular hypothesis explain an observation made on a "hot" melanoma of a limb, in which occlusion of the blood supply led to a general cooling of the limb during the five minutes of the test, without affecting the temperature gradient between the melanoma and the surrounding skin. A similar experiment conducted with a "hot" hæmangioma led to a rapid fall in the temperature-gradient between the hæmangioma and the surrounding skin and a similar rapid rise when the tourniquet was removed. It is tempting to think that local increases in temperature over lumps may on occasion be due not only to increased blood-supply but also to heat production in the lump itself—either by an increase in its metabolism, or by a decrease in the efficiency of its metabolism, which causes more heat and less energy to be produced. If such a hypothesis were supported by further observations, infra-red thermometry might give a quick method of discovering whether radiation or chemotherapy was influencing a tumour.

CONCLUSION

Infra-red thermometry is a method of clinical investigation which has long been neglected and warrants further study.

The Schwarz thermopile was kindly lent by Messrs. Hilger & Watts, and it is a pleasure to thank Mr. R. Elam for his interest, and his patience in instructing us in the elements of thermal physics. Without his help, and the assistance of the company, this work could not have been done. We are also grateful to the clinical research committee of the Middlesex Hospital for defraying the costs of the work, and to our colleagues at the hospital for their interest and help.

K. LLOYD WILLIAMS
F.R.C.S.
Senior Surgical Registrar

F. LLOYD WILLIAMS
M.B. Cantab.
Research Assistant

R. S. HANDLEY
O.B.E., M.B. Cantab., F.R.C.S.
Surgeon

The Middlesex Hospital,
Mortimer Street,
London, W.1

FURTHER STUDIES OF THE MENSTRUAL STIMULANT

IN 1957 a new smooth-muscle stimulant was found in menstrual fluid.[1] Its solubility properties put it among the group of "lipid-soluble acids" reviewed by Vogt.[2] Its suggested physiological function was that, when liberated by the disintegrating endometrium early in menstruation, it passed partly into the circulating blood and thereby stimulated the myometrium to expel the decidua menstrualis; and it might also cause a temporary increase in the contractile activity of smooth muscle elsewhere. Examination of the plasma of two subjects,[3] and study of the effects of the menstrual stimulant on human and guineapig myometrial preparations,[4] gave results that supported this view. It was further suggested that excessive production of, or sensitivity to, the menstrual stimulant might cause primary dysmenorrhœa.

We can now answer in more detail some of the further questions raised by these findings. Menstrual material provided by over a hundred healthy women and six patients with primary dysmenorrhœa—representing in all about 5000 hours of menstrual flow—has been examined. Details of the methods will be published elsewhere,[5] only the principal results being summarised here.

NATURE OF THE MENSTRUAL STIMULANT

The menstrual extracts were previously known to contain at least two stimulant substances, differing slightly in their solubility and pharmacological properties.[6] By a combination of chromatographic and other methods, *three* components of the menstrual stimulant have now been clearly separated from each other and from most of the inert material in the crude-lipid extracts of menstrual fluid. Each component is itself a stimulant, or perhaps a group of stimulants so similar that they cannot yet be separated. One component is notable for its ability to potentiate certain other stimulants, including, to a small extent, a second component of the menstrual stimulant. These two components are acidic, and can be extracted from organic solutions by $NaHCO_3$, while the third is not. One of the acidic stimulants has some of the properties of a long-chain fatty acid, whereas the other is more soluble in polar solvents. The latter is the most potent of the three components as a stimulant of uterine muscle. Among the substances that have already been described clearly enough for comparison, it most closely resembles irin, extracted from the iris,[7 8] and prostaglandin, which originates in the seminal vesicles [9–11]; but it is probably not identical with either.

SPECIFICITY OF EFFECTS

The main effect is stimulation of the myometrium.

When extracts containing all three components of the menstrual stimulant were injected intravascularly into anæsthetised guineapigs whose body cavities were opened under warm saline, respiration being maintained artificially, the only visible effect was stimulation of the uterus and gastrointestinal tract. In vitro also, both organs were stimulated. By contrast, whereas human myometrial preparations in vitro often responded very strongly, only feeble effects were seen on human gastric or intestinal muscle. This accords with the very small increase in gastrointestinal activity during menstruation.[12]

Tests on other tissues and organs showed little or no effect. The clotting-time of guineapig or human blood was unaffected; the blood-pressure of the anæsthetised cat was only slightly and transiently decreased [13]; the beat of the perfused rabbit or

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guineapig heart was either unaffected or only slightly and transiently weakened; the permeability of the blood/aqueous and blood/cerebrospinal fluid barriers of the rabbit to *p*-aminohippurate was unaltered [14]; and intramuscular injection into conscious guineapigs had no obvious effect. Subcutaneous injection of 5 mg. of a relatively crude extract containing all three components of the stimulant had no effect on a man, apart from causing very slight local soreness.

The effects of the menstrual stimulant thus seem to have the degree of specificity appropriate to its supposed physiological function.

MENSTRUAL STIMULANT AND PRIMARY DYSMENORRHŒA

It is well known that if a woman normally subject to primary dysmenorrhœa fails to ovulate in a particular cycle, the following period is often painless. Artificial suppression of ovulation often has the same effect. We have not yet had the opportunity of testing for the presence of menstrual stimulant or its precursors in endometrial curettings from such cases; but it has been stated [15] that, in normal cycles, substances with the properties of the menstrual stimulant appear in the endometrium mainly after ovulation. The absence of pain at the next menstrual period after an anovular cycle might well be explained by the absence of menstrual stimulant.

The uterine contractions of dysmenorrhœa have been alternatively thought to be caused by vasopressin.[16] Our hypothesis does not necessarily exclude such a possibility; but there is no definite evidence of any increase in vasopressin secretion during the menstrual period. In one subject in whom apparently normal menstrual cycles coincided with lactation from the first month post partum,[17] the milk-ejection reflex, which is a sensitive indicator of circulating oxytocin, occurred spontaneously —i.e., apart from the suckling stimulus—no more frequently during menstruation than at other times. Milk ejection is accompanied by antidiuresis,[18] showing that oxytocin and vasopressin are secreted together. This instance therefore does not support the theory that dysmenorrhœa is caused by vasopressin.

If dysmenorrhœa is caused by excessive action of the menstrual stimulant, either an unusually large amount of it might be produced or the myometrium might be abnormally sensitive. In the former case, unusually large amounts might also be found in the menstrual fluid, and in either case dysmenorrhœa would be an exaggeration of a normal process. Alternatively, some different stimulant might be produced in dysmenorrhœa.

In an attempt to decide between these possibilities, the subjects—all healthy students—were asked to indicate whether or not they had experienced any notable uterine pain. This was recorded in 16% of eight hundred specimens; but the amount of menstrual stimulant in the 16% was not significantly different from the others. Next, material was collected from five cases of severe incapacitating dysmenorrhœa. Each of these specimens was matched by a normal control, as nearly as possible identical in all known variables, such as the day of the period, the duration of flow represented, and the type of absorbent material used.

The amount of total lipid extracted by the usual method differed only insignificantly—5·17 mg. per hour of flow in the dysmenorrhœa specimens and 4·24 mg. per hour in the controls—but the stimulant potency per unit weight of lipid was half as much again in the dysmenorrhœa samples as in the controls. This difference was not much greater than might be found between normal batches of specimens collected at random; but as every effort was made to eliminate known causes of variation, the difference may be suggestive. The distribution of the stimulant potency among the various fractions of the extracts showed no difference, thus suggesting that no abnormal lipoid stimulant was present. The sixth case, though presenting as dysmenorrhœa, was atypical in clinical detail and had failed to respond to treatment, and the gynæcologist suspected a psychological cause. The extracts in this case about a quarter of the normal stimulant potency.

ANTISPASMODICS AND THE MENSTRUAL STIMULANT

Dibutamide (ambucetamide), an antispasmodic from which some benefit has been claimed in dysmenorrhœa,[19] inhibited the effect of the menstrual stimulant on human myometrial preparations in vitro, and it also inhibited the effect of vasopressin.[20]

Atropine, which is sometimes included in remedies for dysmenorrhœa but which is not generally considered a powerful agent for this purpose, had only a small inhibitory action on the menstrual stimulant in vitro.

Patulin has been claimed to antagonise the stimulant actions of irin [8] and prostaglandin [11] by reason of a structural similarity, and it also inhibited the effect of the menstrual stimulant more than it did that of pitressin; but it was difficult to separate this pharmacological effect clearly from its generally toxic effects.

δ-dodecalactone, which inhibits irin,[8] did not inhibit the menstrual stimulant.

Other spasmolytics have been tested, but a specific pharmacological antagonist to the menstrual stimulant has not yet been found.

SUMMARY

The menstrual stimulant, extracted from material provided by over a hundred healthy subjects, has been found to contain three clearly separable component stimulants. Their principal effect in vivo is probably on the myometrium.

Menstrual fluid from subjects who complained of mild dysmenorrhœa contained the same amount of menstrual stimulant as did subjects who did not complain, but fluid from five cases of severe typical primary dysmenorrhœa contained about 50% more than did control samples.

Several spasmolytic and other drugs were tested and found to inhibit the effect of the stimulant in vitro to varying extents.

We wish to thank Prof. R. A. McCance for giving us every facility in the M.R.C. Department of Experimental Medicine, Cambridge, where most of this work was done, during the tenure by V. R. P. of a personal grant from the Medical Research Council. We also wish to thank Miss J. E. Bottomley, Mr. O. Lloyd, and others for providing the myometrial samples, and for referring the severe dysmenorrhœa patients to us; Miss A. Smart, A.M.W.I., for arranging the collection of most of the specimens; others who have given invaluable help in this respect; and Dr. N. Ambache for gifts of irin and δ-dodecalactone.

V. R. PICKLES
M.A., M.D. Cantab., D.C.H.
Senior Lecturer in Physiology

H. J. CLITHEROE
B.SC. Sheff.
Allen & Hanburys Research Student

Department of Physiology,
The University,
Sheffield, 10

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Reviews of Books

The Viruses

Editors: Sir MACFARLANE BURNET, O.M., F.R.S., director, Walter and Eliza Hall Institute of Medical Research, Melbourne; W. M. STANLEY, University of California Virus Laboratory, Berkeley. New York and London: Academic Press. 1960. Vol. 1. Pp. 609. 118*s*. Vol. 2. Pp. 408. 93*s*.

THE three volumes, now completed, represent a vast undertaking—to present what is known of the biochemical, biological, and biophysical properties of viruses. Volume 1 is concerned with general virology, volume 2 with plant and bacterial viruses, and volume 3 with animal viruses.[1] Throughout, the focus is on the viruses themselves and their effects on cells, rather than viruses as agents of disease. This attitude is justified on the ground that viruses are the smallest biological units which show the characteristics of living organisms, and as such they offer a route to the understanding of living processes in biophysical and biochemical terms.

Volume 1 is notable for an outstanding contribution by S. S. Cohen on the structural and chemical architecture of host cells, with special reference to the synthesis of polymers. This is a chapter (of 188 pages) which could be read with profit by all biologists concerned with the biochemistry of cells and cell organelles. It does not make easy reading but it gives a picture of the lines of future research and is therefore intensely rewarding. Other valuable chapters concern the comparative chemistry of plant (H. Fraenkel-Conrat), bacterial (E. A. Evans), animal (W. Schäfer), and insect (G. H. Bergold) viruses.

Volume 2 contains many admirable chapters in which the authors have succeeded in describing their esoteric and highly specialised subjects in comprehensible terms. In particular, the contributions by A. Lwoff and by G. S. Stent on bacteriophage multiplication, C. Levinthal on bacteriophage genetics, and F. Jacob and E. L. Wollman on lysogeny are very carefully written and fully stocked with information and references. Altogether, *The Viruses* is an essential reference work for any laboratory interested in virus research.

A History of the Nursing Profession

BRIAN ABEL-SMITH, PH.D. London: Heinemann. 1960. Pp. 290. 30*s*.

DURING the past century nursing has been successively a menial and unskilled trade, an unremunerative vocation, and a profession in its own right. Many books have been written about this evolution, but for the most part they describe the role of particular individuals, or the changes in certain hospitals. Dr. Abel-Smith's study is probably the broadest yet published, for it surveys the antecedents of the organisation and administration of the profession in this country, and is concerned with statistics rather than personalities, Government reports rather than private diaries.

Beginning with a period when Sir James Paget could pronounce the nurses at even a London teaching hospital "dull, unobservant and untaught" (though it seems that the sisters were usually "widows in reduced circumstances"), Dr. Abel-Smith describes the introduction of training methods. They were applied first for nurses at voluntary hospitals, and later, at poor-law infirmaries. (The death, from neglect, of a pauper in Holborn Workhouse in 1864, prompted an investigation by *The Lancet*. Public attention was focused on an appalling state of affairs to an extent which caused Miss Nightingale to acknowledge that she was "much obliged to that poor man for dying"). Later chapters deal with the founding of the first major professional organisation, the British Nurses Association, and the battle for registration. A bill to register nurses was laid before Parliament every year from 1904 to 1914, but failed because doctors, and nurses themselves, were divided in their support of it. Not until 1919 did it pass into the statute-book.

Finally came the problems which have arisen under the National Health Service Act, and Dr. Abel-Smith comments pertinently on the position of a profession which has grown up in a strange way on traditions drawn partly from the Army, partly from religious orders, and partly from public schools for girls. Several nations which originally modelled the training of their nurses on the British pattern have in recent years discarded it for a new system: it may be that changes are overdue in this country too.

1. See *Lancet*, 1959, ii, 548

Differential Diagnosis of Yaws

W.H.O. Monograph Series no. 45. C. J. HACKETT, M.D., F.R.C.P., World Health Organisation, Geneva; L. J. A. LOEWENTHAL, M.D., M.R.C.P., dermatologist, General Hospital, Johannesburg. Geneva: W.H.O. London: H.M. Stationery Office. 1960. Pp. 88. 17*s*. 6*d*.

THIS very welcome contribution to a subject by no means always easy is to be regarded as a companion volume to Dr. Hackett's *An International Nomenclature of Yaws Lesions*, which appeared in 1957. It is hardly necessary to say that this too is a first-class piece of work distinguished, as was its predecessor, by magnificent and characteristic photographs. Only illustrations of diseases likely to be confused with those of yaws have been selected. Among the skin conditions which may be mistaken for yaws, those causing lesions of the palms and soles are the least understood and most troublesome.

This book will appeal mostly to the field worker, especially in the later stages of an eradication campaign when the manifestations of yaws have disappeared as the result of mass penicillin treatment, for it is then that many lesions not due to yaws become prominent.

The subject matter is conveniently divided into three headings: lesions likely to be confused with early yaws lesions; those likely to be confused with yaws hyperkeratosis; and those likely to be confused with late yaws lesions. In the first category are impetigo contagiosa, ecthyma, scabies, chigger lesions, leprosy, tropical ulcer, lichen spinulosus, pityriasis rosea, psoriasis, mycosis, phrynoderma, drug eruptions, sickle-cell anæmia, and tuberculous dactylitis; in the second, pitting, plantar thickening and fissuring, callosities, plantar warts, and rat bites; and in the third, tropical ulcer, granuloma venereum, cutaneous tuberculosis, perforating ulcers, cutaneous leishmaniasis, blastomycosis, depigmentation, osteomyelitis, and onchocerciasis.

This booklet should remain for many years the *Ultima Thule* in the differential diagnosis of yaws.

A Textbook of Gynecology

LAMAN A. GRAY, M.D., F.A.C.S., F.A.C.O.G., associate professor of obstetrics and gynecology, University of Louisville Medical School, Kentucky. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960. Pp. 470. 124*s*.

Dr. Gray and his publisher have combined to produce a textbook of originality and merit. He has selected his material carefully and presented a clear, precise, and balanced summary of modern gynæcological practice. An attractive and lucid style never leaves his meaning in doubt.

Throughout the emphasis is on a proper understanding of basic gynæcological pathology, but careful attention is paid to the mounting evidence that emotional factors can cause certain disturbances in the female genital tract. Although the standard is everywhere high certain sections deserve special mention. In the opening chapter the correct relationship between gynæcologist and patient is discussed with sensitiveness and a deep understanding of women. The chapter on benign and malignant conditions of the cervix is very effective. Beginning with obviously benign lesions, Dr. Gray passes to an examination of pre-malignant conditions, next to carcinoma-in-situ and its cytological diagnosis, and finally to frank invasive carcinoma. The photomicrographs, black and white and colour, are well chosen. In this chapter and throughout the book the photomicrographs are large enough to be seen clearly, and the colour reproduction is true. There is a comprehensive and well-balanced account of the place of hormone therapy in gynæcological practice. The chapter on diseases

of the ovary is full and authoritative and again aptly and beautifully illustrated. Certain common gynæcological operative techniques are described and further clarified by half-tone drawings specially prepared for the book.

At the end of each chapter are a few well-chosen references, some historical, some experimental, and some recent clinical articles; and they are drawn from the European as well as the American literature.

In relation to the rest of the book a little more might have been said about prolapse and its operative treatment. The section on sterility might be improved by more attention to the clinical approach and management; this chapter tends to be a catalogue of possible investigations and treatments. In the treatment of uterine fibroids myomectomy is not given enough prominence.

This beautifully produced book deserves inclusion in all departmental libraries as an outline for undergraduate and postgraduate teaching.

Trauma in the Aged

Editor: EDGAR M. BICK, M.D., attending orthopædic surgeon, Mount Sinai Hospital, New York. New York and London: McGraw-Hill. 1960. Pp. 524. 124*s*.

"WHEN youth is fallen, there's hope the young may rise: but fallen age for ever hopeless lies". Thus the poet of a hundred years ago: and certainly the statistics quoted in this book bear out his opinion. In the United States, the death-rate due to accidents is, for the population under 65, approximately 50 per 100,000. In the case of the "senior citizens" (as they are here termed) the rate is almost four times as great. Those of 65 and over comprise only 8% of the United States populace; but they contribute 29% to the total number of accident deaths each year.

Eighteen authors, most of them from New York hospitals, are represented in this book, which is concerned both with the general problems of old people who have been hurt, and with the management of specific injuries. Some readers may wish that more articles on the general subject had been included, and that such matters as analgesics, nursing techniques, and the treatment of thromboembolic complications had been considered. The sections, too, which are devoted to particular injuries might have been less comprehensive but more relevant to geriatrics: there is an otherwise excellent chapter on the crush syndrome, in which only two brief paragraphs are of special significance in the elderly patient.

This book can be recommended as a practical and conservative exposition of those methods which are used in North America to restore to health old people who have had an accident. They are very similar to those practised here: if he could have foreseen their evolution, George Crabbe (who lived to be a very senior citizen indeed) would, perhaps, have recast his lines.

Active Alerted Posture

W. E. TUCKER, F.R.C.S., consultant orthopædic surgeon, Royal London Homœopathic Hospital. Edinburgh: E. & S. Livingstone. 1960. Pp. 64. 10*s*. 6*d*. (17*s*. 6*d*. in de luxe edition.)

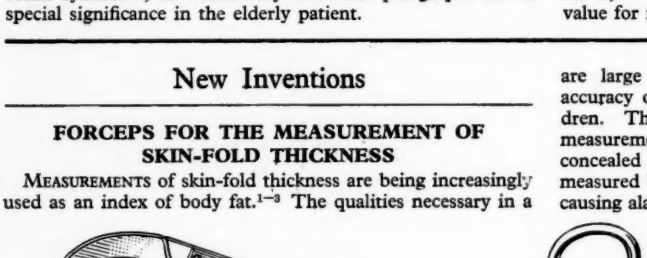
IN this monograph, by a surgeon who has often treated internationally famous athletes, many cases of arthritis, rheumatism, and disc degeneration are attributed to bad posture. Sitting or standing in a slumping fashion throws, he believes, an unnatural strain on various joints which will eventually degenerate. He advocates the acquisition of a habit of standing in an "active alerted position" ("top of head trying to touch the ceiling: navel press-buttoned to the spine: buttocks pinch-proof, and ground gripped with the toes") and claims that many physical and some emotional disorders can be prevented or cured in this way. His book is addressed to physiotherapists and trainers as well as to doctors, and is certainly much more convincing, and more easily understood, than many others which have been written on the same theme.

Rose and Carless' Manual of Surgery (19th ed. London: Ballière, Tindall & Cox. 1960. Pp. 1389. 84*s*.).—Rose and Carless is an old friend which has received a further and vigorous rejuvenation in this edition, edited by Sir Cecil Wakeley, Mr. Michael Harmer, and Mr. Selwyn Taylor. Happily unity has been restored after its recent dichotomous two-volume adventure. There has been much and excellent rewriting by the editors and their fifteen contributors. May we plead for still further pruning in the next edition, beginning with the omission of the illustration of classical eponymous ligations for aneurysm, the substitution of the coloured illustration of a breast sarcoma for something more useful, and less preoccupation with syphilis (which has 46 references in the index) in exchange for greater interest in diabetes (which has 1)? In these days of high prices, this book is excellent value for money.

New Inventions

FORCEPS FOR THE MEASUREMENT OF SKIN-FOLD THICKNESS

MEASUREMENTS of skin-fold thickness are being increasingly used as an index of body fat.[1–3] The qualities necessary in a calliper designed for measuring subcutaneous-tissue thickness have been defined,[4] but the instruments available commercially are large and cumbersome. Although they permit great accuracy of measurement they are frightening to small children. The instrument described here, designed to make measurements to within 0·25 mm., is small enough to be concealed in a coat pocket. With it fat thickness can be measured below the angle of the scapula in any child without causing alarm.



The forceps comprises a pair of box-jointed handles, one being connected to a curved jaw which is fixed, and the other to a similar jaw which can move freely on a second hinge. The faces of the jaws are rectangular (6×15 mm.). When they are approximated by closing the handles, increasing pressure is exerted between the jaws, and this is so adjusted that, when two pointers close to the box joint of the forceps handles are in line, the force between the jaws is 900 g., as recommended by Edwards et al.[4]

This instrument has been made of stainless steel to our design by Chas. F. Thackray, Ltd., 10, Park Street, Leeds, 1.

D. VEREL
M.A., M.D. Cantab., M.R.C.P.
A. B. KESTERVEN
Sheffield Region Cardiovascular Centre, City General Hospital, Sheffield, 5

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THE LANCET

LONDON 29 OCTOBER 1960

Government of Greater London

FIFTEEN years ago Prof. PATRICK ABERCROMBIE wrote [1]:

"Give a man and his wife a first-rate house, a community, and occupations of various kinds reasonably near at hand, within a regional framework which enables them to move freely and safely about, to see their friends and enjoy the advantages of London; add to these a wide freedom of choice, and they will not grumble in the years immediately following the war."

ABERCROMBIE'S plan, though not itself dealing with government, would have called for some kind of regional authority with powers of direction and fiscal control. No such authority has been set up; and if in 1960 the Londoner and his wife are still grumbling, who shall blame them? The latest and most impressive approach to this problem has been made by a Royal Commission, under the chairmanship of Sir EDWIN HERBERT, which was appointed in 1957 to examine the system of local government in the Greater London area, and which has now reported.[2]

The report is informed by a conviction that the people of this area lack homogeneity: "There is no strong social unity within the Counties of London or Middlesex." The commissioners admit ruefully that any solution it offers is bound to arouse strong opposition from some quarter. The solution it does offer is founded on two main proposals:

1. That the primary unit of local government in the Greater London area should be the "Greater London borough" having (save for the city of London) a population of between 100,000 and 200,000.

2. That an authority—the Council for Greater London—with limited functions should be established to cover the area of the proposed new boroughs.

The duties of the *Greater London boroughs*, of which there would be some 52, would include the following:

To receive and consider applications for planning consent within the borough area; to be the highway authority for all except main roads, with responsibility as agent for the Council for construction work on main roads; to be the housing authority within the borough boundaries; to act as education executive with day-to-day management of schools, including the school health services, in its area; to be fully responsible for the whole range of personal health, welfare, and children's care services; to undertake refuse *collection*; to supervise parks, art galleries, and museums; to operate the Food and Drugs Acts and regulations; and to control atmospheric pollution.

The new boroughs would perform their functions as of right—that is, not as delegated functions—and without overlapping with or duplication by the wider Council.

The duties of the *Greater London Council* would include:

Education planning and control; town and country planning as the local planning authority; housing to supplement needs not met by the boroughs and taking over existing Greater London L.C.C. housing estates which should, where appropriate, ultimately be given to the boroughs in which the houses are sited; traffic management; highway planning and main-road construction and maintenance; ambulance services and fire services; sewerage and refuse *disposal*; and the appointments of coroners (except in the city of London).

The members of both the borough councils and the Greater London Council would be elected by direct public ballot for three years. Each borough council would have about 100 members; while the Greater London Council would be constituted on the basis of one member to represent each parliamentary division. The commission's revolutionary proposals would have the effect of putting out of existence the London and Middlesex county councils, "demoting" two county boroughs (East and West Ham), and annexing substantial urban parts of Essex, Kent, and Surrey.

The Commission seems to have been impressed by the unhappy relations between some county authorities and local councils, which have not recovered from losing services to the county. It also seems to be convinced that services provided from the town hall are bound to be better and more acceptable to the burgess than the same services provided by the local branch of the county department. Where the medical officer at the town hall is also the county's area medical officer, the Commission has little use for him. Throughout the report the emphasis is much more on organisation than on the quality of people working in the organisation. Yet the quality of these people—and especially of the highly-trained—is a vital factor in the standard of service. When this is realised better in town and county hall, and the realisation is acknowledged in improved salary scales, there may be a halt to the damaging migration from local government of engineer, architect, doctor, nurse, and psychiatric social worker.

In formulating its proposals the Commission was apparently much influenced by the appalling traffic conditions on the roads; by the continuing need for new houses; by the difficulty of clerks in getting from home to office and of factory workers in securing a decent home not too far from their jobs; by the sprawl of urbanisation outwards from Central London without good really *local* government; and by the increasing needs of the increasing number of old people. As regards public health, the report holds promise of improvement through the reunion of sanitation, hygiene, domiciliary health services, midwifery, health education, preventive vaccinations, "meals on wheels", provision of nursing appliances and laundry, surveillance of isolated old people, chiropody, and mental health and welfare services under one management, with the housing department next door and the home nurse a few steps away.

Early in the report the Commissioners complain that good people will not come forward to be borough

1. Abercrombie, P. Greater London Plan. H.M. Stationery Office, 1945.
2. Royal Commission on Local Government in Greater London 1957–60. Cmnd. 1164. H.M. Stationery Office. 28*s*. 6*d*.

councillors, and they express the hope that the new scheme will revitalise local government. The commission's blood-transfusion could hardly fail in time to improve the arteries and the circulation of London's local government; whether the tissues were revitalised would depend on the quality of the new blood.

Ethionamide

ISONIAZID, the most potent of the anti-tuberculosis drugs so far discovered, is a derivative of isonicotinic acid. Another derivative, isothionicotinamide, was synthesised in 1951 by LEE in the U.S.A., and in the following year by LIBERMANN in France. In-vitro studies showed that it was about 400 times less active than isoniazid on tubercle bacilli; but its in-vivo activity was considerably greater.[1 2] Unfortunately, it appeared to be totally ineffective in man.[3] Further homologues were prepared by the French workers; and finally 2-ethylisothionicotinamide (ethionamide) was selected for clinical study, as it was found to be 30 times more active in vivo than the original thioamide, and no more toxic. The laboratory experiments leading up to its first clinical trial have been summarised by RIST et al.[4] It is active against isoniazid-resistant bacilli, and ethionamide-resistant strains are sensitive to isoniazid. There is, however, a suggestion of cross-resistance between ethionamide and thiosemicarbazone; many ethionamide-resistant strains have been found resistant also to thiosemicarbazone, but strains resistant to thiosemicarbazone after in-vitro passage have been sensitive to ethionamide. Ethionamide-resistant cultures have been isolated from a patient who had received large doses of thiosemicarbazone; but they have also been obtained from patients not known to have previously received either thiosemicarbazone or ethionamide. Studies of the bacterial populations in infected mice suggested that treatment with ethionamide alone would lead to the development of resistant populations, but that this could be avoided if streptomycin or isoniazid was used as well.

The first clinical trials of ethionamide were started by BROUET in 1957; and in 1958 he reported his findings at a meeting of the International Union against Tuberculosis.[5] The drug appeared effective in previously untreated disease in doses of 1 g. a day; but strains of diminished sensitivity appeared in the sputum of some patients.[6] A small group of 8 patients was treated with ethionamide plus isoniazid; after three months only 1 patient was still sputum-positive, the culture being sensitive to both drugs. HUTTON and TONKIN[7] treated 7 African patients who had acute pulmonary tuberculosis with 1 g. of ethionamide daily in four divided doses, and 1 g. of streptomycin daily for six months. Of the 6 examined bacteriologically after six months, only 1 gave a positive culture; this strain was resistant to both ethionamide and streptomycin. There have been several other reports of clinical experience with ethionamide, mainly from France; but they have added little to our knowledge of the value of the drug in previously untreated patients, for the trials have not been carried out in such a way that the results can be compared with those of the well-tried combinations of streptomycin, *p*-aminosalicylic acid (P.A.S.), and isoniazid.

While treatment with ethionamide alone of newly diagnosed patients who are not seriously ill is certainly defensible, there may be more doubts about the justifiability of treating acutely ill patients with this new drug together with isoniazid or streptomycin. If the new one fails to protect against resistance to the other, the patient's chances of complete recovery may have been reduced. In Great Britain the best available chemotherapy can be given to all who need treatment; and it could be argued that it is unjustifiable in such circumstances to treat a patient with a combination of drugs that may be less effective. In countries where, owing to lack of money and facilities, only few can receive the best, such a trial might be more defensible; and if the new drug offered considerable advantages over P.A.S. as a companion for isoniazid in large-scale treatment, the investigation could be considered fully warranted. But even in these circumstances it would be warranted only if it were planned and executed in such a way that a clear answer could reasonably be expected to emerge. All too often in the past, uncritical clinical experiments in chemotherapy have not only put patients needlessly at risk but have also hampered the progress of knowledge. We hope that well-planned large trials of ethionamide with isoniazid or streptomycin will be carried out soon; for until these are completed the potential benefit of this new drug cannot be determined.

More is known about its value in treating patients with tubercle bacilli resistant to the three main drugs. In such patients there is much less ethical difficulty; for they stand to lose very little, if anything, by taking part in well-conducted trials. SOMNER et al.[8] administered tetracycline (4 g. daily) as the companion drug in 7 cases of advanced disease with sputum cultures resistant to streptomycin, isoniazid, and P.A.S. The patients received 1 g. of ethionamide in two doses of 500 mg. daily. In 5 there was an initial effect on the bacillary content of the sputum, but ethionamide-resistant cultures then appeared; in 1 the sputum remained occasionally positive up to seventeen weeks, but resistant strains were not detected; in only 1 did the sputum become persistently negative on culture.

The clinical trials committee of the research committee of the British Tuberculosis Association undertook a preliminary clinical study of ethionamide in 1959, at the request of a pharmaceutical firm. They treated patients with advanced disease and cultures resistant to the three main drugs with ethionamide (0·5 g. daily) and either cycloserine (0·5–1·0 g. daily) or pyrazinamide (2–3 g. daily).

1. Gardner, T. S., Wenis, E., Lee, J. *J. org. Chem.* 1954, **19**, 753.
2. Libermann, D., Rist, N., Grumbach, F. *Bull. Soc. Chim. biol., Paris*, 1956, **38**, 231.
3. *Quart. Progr. Rep. V.A. Chem. Tuberc.* 1955, **10**, 44.
4. Rist, N., Grumbach, F., Libermann, D. *Amer. Rev. Tuberc.* 1959, **79**, 1.
5. Brouet, G. *Bull. Un. int. Tuberc.* 1958, **28**, 228.
6. Brouet, G., Marche, J., Rist, N., Chevallier, J., Le Meur, G. *Amer. Rev. Tuberc.* 1959, **79**, 6.
7. Hutton, P. W., Tonkin, I. M. *Tubercle, Lond.* 1960, **41**, 253.
8. Somner, A. R., Ross, J. D., Macleod, H. M., Stewart, S. M., Horne, N. W., Crofton, J. W. *Brit. med. J.* 1959, i, 486.

At the time of their preliminary report [9 10] 13 out of 25 patients in the pyrazinamide group had negative cultures at the end of the third month, and 8 out of 15 at the end of the sixth month, of treatment. The corresponding figures in the cycloserine group were 18 out of 21 and 7 out of 11. In the pyrazinamide group (29 patients) cultures with decreased sensitivity to pyrazinamide were isolated in 9 cases and to ethionamide in 5 cases. In the cycloserine group, cultures with decreased ethionamide sensitivity were found in 9 of 23 patients. Sensitivity tests were done on 26 patients in the pyrazinamide group before treatment was begun. In 2 cases the strains were 4 and 8 times less sensitive to ethionamide than the standard test strain, and in 3 the strains were from 4 to 32 times less sensitive to pyrazinamide.

It seems clear that neither of the combinations used was highly effective in this type of case, although the finding that half the patients had negative cultures at six months is sufficiently promising to justify further investigation, especially as the dose of ethionamide was only half that originally used by BROUET.

This study was not devised to compare the effects of these two drug combinations, but only to gain experience of the new drug and to assess whether it was worth extended trial. Further trials now being carried out by the research committee of the British Tuberculosis Association are designed so that drug combinations can be compared, using ethionamide with cycloserine in one group and ethionamide, cycloserine, and pyrazinamide in another, with larger doses of ethionamide than in the pilot study. Ethionamide is also being administered with streptomycin to patients with cultures resistant only to isoniazid and P.A.S. These controlled, cooperative investigations, which take considerable time and labour, will eventually provide much information of value for treating those in whom initial treatment has failed.

Ethionamide, though a promising drug, has one important disadvantage. Many patients cannot tolerate it in more than small doses, because of anorexia, abdominal discomfort, and nausea and vomiting. BROUET [5 6] reported that only 55 of 102 patients attempting to take 1 g. daily had no symptoms of intolerance; 6 had transient anorexia, and 29 intense persistent anorexia; and 5 could not continue the drug at all. BROUET recommended that treatment should begin with small doses and the full dose of 1 g. be reached in stages. 6 of the 7 patients treated by SOMNER et al.[8] with 1 g. had troublesome symptoms needing reduction of dose or temporary interruption of treatment. SOMNER [11] later carried out a controlled trial with daily doses of 0·5, 0·75, and 1·0 g. daily. With the smallest dose there was very little intolerance, but interruptions of treatment became commoner as the dose increased. Enteric-coated tablets have been used in an effort to reduce the gastrointestinal symptoms; but there is no satisfactory evidence that they do so, and the coated tablets appear to give more variable and lower serum levels. The drug has also been given rectally by suppositories, which are claimed to give rise less commonly to intolerance [12]; but symptoms of intolerance still occur with rectal administration, suggesting that the effect is not a local one on the stomach.

It should not be assumed that drug intolerance is the same the world over. LAUCKNER [13] studied tolerance to ethionamide in 21 African patients in Nigeria. They received from 625 to 1250 mg. daily in two doses, according to weight (approximately 15–17 mg. per kg.), for twelve weeks. The patients were not in hospital, but attended a clinic weekly, except for 7 who missed one to four weeks' treatment for financial or domestic reasons. No patient had to stop taking the drug or have the dose reduced because of symptoms of intolerance. 9 had no symptoms at all; 3 had mild, transient diarrhœa, possibly unassociated with the drug; 6 had anorexia; and 4 reported more persistent abdominal pain or vomiting. Of the 7 African patients treated by HUTTON and TONKIN [7] in hospital in Uganda with 250 mg. four times a day, none had any troublesome symptoms. There is a suggestion therefore that tolerance to ethionamide, as to other drugs, may vary considerably between races or even between hospitals. The apparently common intolerance in Europe should not prevent full investigation of the drug elsewhere. No other troublesome toxic effects have been reported. A metallic taste in the mouth may be complained of; and excessive salivation and sore mouth or tongue have been reported in Africans, improving when yeast was given.[13] Gynæcomastia appeared in 3 patients receiving ethionamide and streptomycin, receding with testosterone treatment.[7] Probably a few additional toxic reactions will be reported as the drug becomes more widely used; but on the present evidence it appears to be a safe, though often unpleasant, one to take. The mechanism by which the gastric symptoms are produced is unknown. It should be much more fully investigated, for if a way can be found to make ethionamide more tolerable it may turn out to be a valuable drug. Certainly at present the evidence is insufficient to justify its use, other than in carefully controlled trials, in newly diagnosed cases of tuberculosis; and the poor tolerance of it severely limits its value in those unfortunate patients whose physicians' mistakes, or whose own lack of cooperation, have led to failures of treatment.

Professions Supplementary

As usually understood, a profession possesses (1) a body of knowledge or art, which it seeks to expand, and (2) a standard of conduct which goes beyond the performance of specific duties. In one profession the knowledge or technique may be more important; in another the ethical code. Thus CARR-SAUNDERS and WILSON [14] said that in the typical profession the technique is founded on basic inquiry. The work of doctors and dentists, for example, is founded on science, and demands a long specialised intellectual training. On the other hand, the work of nurses and midwives is founded only on the *application* of a science; and the claim of

9. Somner, A. R. *Tubercle, Lond.* 1960, **41**, 309.
10. Riddell, R. W., Stewart, S. M., Somner, A. R. *Brit. med. J.* Oct. 22, 1960, p. 1207.
11. Somner, A. R. *Tubercle, Lond.* 1959, **40**, 457.
12. Veran, P., Moigneteau, C., Trichereau, R., Rist, N. *Rev. Tuberc., Paris*, 1959, **23**, 454.
13. Lauckner, J. R. *Tubercle, Lond.* 1960, **41**, 367.
14. Carr-Saunders, A., Wilson, P. A. The Professions. London, 1933.

these vocations to be professions is sustained by their heavy responsibilities rather than their academic learning. The nurse and midwife may not be scientists, but they certainly hold positions of trust. The present tendency of more and more groups to adopt a professional organisation can be criticised on the ground that many of them are more closely equivalent to the medieval craft than to professions as formerly recognised; but for our part we welcome the trend towards professionalism for two reasons. First, because people who take pride in their status always raise their standards; and, secondly, because public services staffed by members of independent professions are far more likely to thrive than services staffed by people who are primarily State employees.

This week the Royal Assent is likely to be given to an Act setting up a professional organisation for seven new "professions supplementary to medicine". Eleven years have passed since committees were set up, under the general chairmanship of Sir ZACHARY COPE, to consider what should be done; and the delay following the Cope report [15] has been due to differences of opinion about the composition and control of the professional licensing boards. This delay, however, has had at least one good effect, in that it has enabled the collective name to be changed from "medical auxiliaries" to "professions supplementary to medicine"—a happier (though still imperfect) description of a group of devoted servants of the public. Doctors know better than most the value to the community of chiropodists, dietitians, occupational therapists, physiotherapists, radiographers, and remedial gymnasts; and we join with the public and Parliament in approving the status now given to these professional colleagues. We may, however, extend a special word of welcome to that group whose work the public never see but who are in a special sense our indispensable helpers—namely, the medical laboratory technicians. They bear the brunt of routine clinical pathology, and their role in research is also important.

To all the professions supplementary to medicine, their new status is both an achievement and a challenge. Standards and traditions will have to be established and maintained, so that they may do still better what they are already doing well. Professional status should prove a step forwards as well as upwards—not only, we hope, towards proper financial and other recognition but also towards greater opportunities for service.

15. See *Lancet*, 1951, i, 895.

Annotations

HARVEIAN CHALLENGES

LAST week's Harveian oration was given by Sir Francis Fraser, who, like William Harvey, was physician to St. Bartholomew's Hospital. Fraser's main appointment, however, was one of a new kind; and he thinks of the institution of professorial units in 1920 as a return to the Harveian way of solving biological problems by observation, experiment, and measurement. His commentary on the fifty years since he qualified ended with a highly topical appeal for a biological approach to health and disease.

Though there were several earlier examples in Germany and the United States, the first comparable opportunities for clinical research in this country we owe to the Royal Commission for University Education in London, under Lord Haldane, which recommended the appointment of professors who would give most of their time to teaching and research, working through hospital units. Because this report came out just before the first world war, no immediate action was taken; but by the end of 1921 there were in London five units in medicine and four in surgery, controlled by full-time professors or part-time directors; and outside London Cardiff had established medical and surgical units. Clinicians were now eager as never before to use any help they could get from physiologists and biochemists and their quantitative methods; and in those days it was members of the staff of the professorial units who carried out these procedures. The units in London were established just in time to apply important advances in the basic sciences, and Sir Francis regards their establishment as "the first concerted action in this country to enable clinical medicine to meet the challenge of William Harvey's great achievement by training young clinicians to be clinical scientists".

In many respects the Goodenough report in 1944 carried on from the recommendations of the Haldane Commission; and now there are only a few medical schools without a full-time professor of medicine directing a unit with full-time assistants, wards, and laboratories. The number of young clinicians trained to utilise the methods of the basic sciences is extremely gratifying, and Sir Francis puts it down to the creation and influence of the university professorial units. But there was one striking difference in the Haldane and Goodenough reports—namely, the emphasis given by the latter to social and preventive medicine and to psychiatry—two closely related subjects. There are still not nearly enough men qualified to have charge of academic departments of social medicine, and in psychiatry there is little if any basic knowledge of how emotional and mental disturbances affect physiological processes. We face also the reverse problems—the effects of illness on the social equilibrium of patients and their families and on their mental and emotional reactions.

At the conference in Chicago last year on postgraduate medical education, it was generally agreed that postgraduate education in social medicine and psychiatry would remain ineffective until undergraduates are trained to appreciate the numerous social and community factors of ill health; "and this," said Sir Francis, "will only be accomplished when the physicians and surgeons themselves set a good example by developing a biological and ecological approach to every patient under their care". Some medical schools have taken steps to introduce the undergraduate to the conditions met with in family practice; but nothing can replace the example the student should be given by all his teachers. As Lord Adrian said in his British Medical Association address of 1959, "it would be a great mistake to think that there can be a general advance without the support of every doctor who has patients to understand". General practitioners and consultants, Sir Francis concluded, are both able to contribute to this advance and to meet this new challenge; and they are more likely to do so if they cooperate both

with each other and with people in public health. " Surely the senior physicians and surgeons of our general hospitals are the persons to take the lead in forming such a partnership, each for its own community. Regular meetings of representatives of the three divisions of the National Health Service, and perhaps of the clergy also, in the area would soon show how each can best help the others and how the hospital and local-authority services can utilise the peculiar experiences of family doctors to supplement their own restricted and specialised training."

RENAL BIOPSY AND AMYLOID DISEASE

IMPORTANT points about renal amyloid disease are underlined by Heptinstall and Joekes [1] in an account of 11 cases proved by renal biopsy. These cases were found in a series of 220 biopsies; and Heptinstall and Joekes question the prevalent belief that amyloid disease is now rare. There was a history of osteomyelitis in 5, of pulmonary tuberculosis in 2, of chronic bronchiectasis in 2, and of rheumatoid arthritis in 1, leaving only 1 in which a presumptive diagnosis of primary amyloidosis was made. In the 2 cases of bronchiectasis and the case of rheumatoid arthritis, the primary disease had persisted and was active when the amyloid developed. In the 2 tuberculous cases there had been no activity for three and ten years. Of the 5 osteomyelitis cases 1 had been active up to a few months before the renal amyloidosis was proved, but in the other 4 there had been no evidence of activity for eight to forty years: 1 patient, with an interval of twenty-five years, had had ulcerative colitis for two years up to a year before the renal biopsy. (Does this suggest that amyloid may complicate ulcerative colitis? Evidence of such an association is sparse; but Werther et al.[2] have collected reports of 6 cases and also record an unexpectedly high incidence in regional enteritis.) The patient with the forty-year interval had been admitted to hospital several times on account of minor illnesses, but proteinuria had not been found until some months before the renal biopsy. Heptinstall and Joekes remark that the apparent absence of proteinuria in some cases for a long time after the underlying lesions had become inactive cannot be taken as evidence against renal amyloid infiltration in this interval; possibly, once started, amyloid deposition progresses very slowly in some cases and much more rapidly in others.

Though in all cases proteinuria was found at the time of biopsy, only 4 patients had had œdema at any time, and in only 2 was this more than slight; none had been present in 2 patients with proteinuria for eight and three years. 2 patients had a much-reduced serum-albumin level, and in only 1 was the plasma-cholesterol over 300 mg. per 100 ml. On the other hand, hypertension was much commoner than in previous series: of the 11 patients, 7 had systolic blood-pressures of 150 or more mm. Hg. Heptinstall and Joekes suggest this may be due to their patients' relatively good general condition; for in previous series the patients commonly had long-standing infection.

Perhaps the most important finding was the good renal function despite the severe infiltration of the kidney, especially the glomeruli, with amyloid. In 9 of the 11 cases, every glomerulus in the biopsy specimen contained amyloid in the capillary tufts: even where the glomerular involvement was extensive the tubules were sometimes not grossly abnormal, but in 3 cases tubular damage was also severe. In 1 of these renal function was so good as to cast doubt on the validity of the renal biopsy as representing the total renal damage; but in this case three different pieces of kidney were taken at the same time and all showed the same changes. Other tests for amyloid, such as the congo-red and gum and liver biopsies, were negative in several of the cases after the onset of proteinuria; and thus renal biopsy emerges as the most certain method of making the diagnosis when the full nephrotic syndrome is not present.

Amyloid disease is a mimic [3] with many vagaries [4]; and its insidiousness is again shown by this series.

1. Heptinstall, R. H., Joekes, A. M. *Ann. rheum. Dis.* 1960, **19**, 126.
2. Werther, J. L., Schapira, A., Rubinstein, O., Janowitz, H. D. *Amer. J. Med.* 1960, **29**, 416.

THE DEVELOPING CHILD

ALTHOUGH there is now reliable information on the results of cross-sectional and serial studies of child populations, regrettably little is known about the important variables in the development of the individual child. For the study of process rather than product, longitudinal investigations of individual children are required; and Prof. Herbert Birch, in a lecture at the Maudsley Hospital on Oct. 12, described some of the findings of his current work at the Albert Einstein College of Medicine, New York.

The clash of views between genetecists and environmentalists is, he believes, being replaced by a more fruitful interest in the interaction between the biological substratum and environmental influence. He has studied the behavioural characteristics of 105 infants, mostly of middle-class, college-educated Americans—a socially homogeneous group being deliberately chosen for the better study of organismic variability. Information was sought on the child's behaviour in natural surroundings, rather than from laboratory tests. Two independent trained observers each spent a day in the household, and their reports were compared with each other and also with that from the parents. There was significant agreement between the two trained observers but still greater agreement between the separate observers and the parents. Thus, provided attention was confined to actual behaviour described and parental interpretations of this were ignored, the parents' reports were valid and reliable. From this information nine separate characteristics of behaviour could be identified in each child: activity level, rhythmicity of function or its absence, response to new stimuli (whether an " approacher " or " withdrawer "), adaptability, intensity of adaptable pattern reaction, threshold of responsiveness, quality of mood, distractability, and attention span and persistence. Comparison of item analysis with protocol analysis showed that there was negligible " halo " effect in these assessments.

Although they varied greatly from child to child, and at different ages related to different basic contents of activities, the formal characteristics remained remarkably constant in each individual child; and after two years some 90% of the children retained their original position on a three-point scale (with an 0·01 level of reliability). This remarkable stability of behaviour seems to persist even after five years, but fewer children have been studied for this period.

The effects on these characteristics of different stresses, such as parental death or separation or birth of sibs, have been studied as they occurred. Rather surprisingly, little effect was found; and, although the *form* of activity may

3. Symmers, W. St. C. *J. clin. Path.* 1956, **9**, 187.
4. *Lancet*, 1958, i, 1378.

have altered, the *style* remain unchanged. The long-term effects of these stresses have yet to be studied. Change in the form of behaviour was greatest in the active, arrhythmic, distractable child.

Professor Birch's careful and objective work has provided a valuable basis for further studies, which may give much useful information relevant to child psychiatry. He has still to analyse the relation of these characteristics to the more complex psychological functions, and the clustering and interrelationship of these aspects of behaviour.

MUTATIONS DUE TO CHEMICAL SUBSTANCES

THE widespread use of radioactive materials both in industry and in medicine, coupled with the development of the nuclear-power industry, has attracted attention to the potential genetic risk of exposure to ionising radiations. The Medical Research Council [1] declared that the dose of man-made radiation to the general population should not grossly exceed the natural background radiation, and should be well below that capable of doubling the spontaneous-mutation rate. The recommendations of the International Commission on Radiological Protection [2] embody maximum allowable doses of radiation from the point of view of preventing both somatic and genetic effects.

The potential genetic effects of ionising radiations have diverted attention from other factors in the modern environment that may produce changes in the mutation-rate and hence give rise to genetic damage. Alexander [3] points out that many chemicals may cause increased mutation-rates in man, and that the possible dangers have been far less scrupulously studied than have the effects of radiation. Most experiments on the mutagenic effects of chemicals have been done on microorganisms, plants, and insects, and very little work has been done on mammals.

The most potent mutagenic chemicals so far discovered are the highly reactive alkylating agents, such as mustard-gas and its derivatives. The epoxy resins, which are used as adhesives for laminated plastic materials, can also act as alkylating agents and are highly mutagenic until they are polymerised in the adhesive. Sterilisation of foods by exposure to enormous doses of ionising radiations is a new technique which may prove a very cheap and effective means of preserving food. Epoxides are known to be formed in irradiated foods, and these may conceivably cause genetic change in the offspring of people regularly eating such foods. Other chemicals known to have mutagenic properties are formaldehyde and some peroxides. Formaldehyde is used in food preservation and in "air purifiers", and peroxides are formed in heated fats and may therefore be contained in fried foods. Mutations in microorganisms have been produced by some antibiotics and hormones, and by some components of weedkillers and contraceptives.

The majority of chemical substances have not been studied for possible mutagenic effects, and even for those so far found to cause mutations there is no information as to the quantities that will double the mutation-rate in man. The so-called "tolerable levels" for the vapours of toxic chemical substances commonly used in industry are determined usually from the doses known to produce acute toxic effects, and only rarely from assessment of the possible long-term genetic effects. Alexander thinks that some industrial "tolerable levels" of chemicals already known to be mutagenic (such as ethylene oxide and ethylene imine) would produce an incidence of genetic damage which would be completely unacceptable if produced by ionising radiations.

The far greater sensitivity of the embryo than of the adult to injurious agents is well known. Thus damage to a fœtus may arise from concentrations of chemicals too low to produce an apparent effect on the mother. The damage in this case is due not to a genetic change but to a direct toxic effect on some of the cells in the developing embryo. This type of risk tends to be overlooked in determining safe doses of potentially toxic substances to which the general public may be exposed.

There is clearly a need for more research into the genetic and embryonic effects of many chemicals commonly used in the home and in industry—particularly of those used in the manufacture and preservation of food. The aim should be not only to identify substances which are mutagenic but also to estimate the magnitude of the effect and to study the uptake, distribution, and metabolism of such substances in the human body. Only thus can the extent to which chemicals are causing mutations in the population be determined and preventive measures taken that are comparable with those against radiation.

1. Hazards to Man of Nuclear and Allied Radiations. H.M. Stationery Office, 1956.
2. Recommendations of the International Commission on Radiological Protection. London, 1958.
3. Alexander, P. *New Scientist*, Oct. 20, 1960, p. 1073.

TRIPARANOL AND CHOLESTEROL

TRIPARANOL ('MER-29') blocks the synthesis of cholesterol from its immediate precursor, 24-dehydrocholesterol or desmosterol. Laboratory animals treated with triparanol have a lowered cholesterol level in the liver, kidneys, blood, and aortic wall, but the level in brain and adipose tissue is unaffected [1]; desmosterol, which cannot normally be detected in mammalian liver and blood, appears in large amounts.[2] Prolonged administration of triparanol to monkeys and other animals effectively lowers blood-cholesterol without serious toxicity.[3]

In man, moderate reduction of blood-cholesterol can usually be achieved.[4] Oaks et al.[5] treated 36 patients with initial cholesterol levels above 250 mg. per 100 ml. After four weeks' treatment, the mean fall of cholesterol was 69 mg. per 100 ml. (S.D. 24). They obtained a maximal effect with 250 mg. triparanol daily; side-effects—nausea and transient albuminuria—developed with larger doses. Hollander et al.[6] treated 89 patients for three to fourteen months and also found that 250 mg. daily was as effective as larger doses. The blood-cholesterol fell in 71 of their 89 patients, the mean fall being 45 mg. per 100 ml.; reduction of cholesterol was greatest in those with high initial levels. Serial investigations showed no toxic effects on the blood or kidneys. Bromsulphthalein retention with a slight rise of alkaline phosphatase was observed in 4 patients in the early months of treatment. These tests soon reverted to normal and liver biopsies showed no evidence of liver damage. 2 patients, receiving 250 mg. triparanol daily, developed a rash which cleared when treatment was stopped and did not recur when treatment

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2. Avigan, J., Steinberg, D., Thompson, M. J., Mosettig, E. *Progr. Cardiovasc. Dis.* 1960, **2**, 525.
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5. Oaks, W., Lisan, P., Moyer, J. M. *Arch. intern. Med.* 1959, **104**, 527.
6. Hollander, W., Chobanian, A. V., Wilkins, R. W. *J. Amer. med. Ass.* 1960, **174**, 5.

was restarted. The fall of cholesterol started after about a week and was greatest after four weeks. The cholesterol rose to pre-treatment levels two to eight weeks after triparanol was discontinued. The total body pool of cholesterol fell during treatment. There was no evidence of adrenal depression, and there was little change in urinary 17-ketosteroid and corticosteroid levels. Other workers have shown that triparanol has mild œstrogenic activity.[7]

Kountz [7] treated 75 patients with 250 mg. triparanol daily. The majority showed a 15-20% fall in cholesterol over the first three months, but the level then ranged upwards over a further three months. This secondary rise of cholesterol was sometimes prevented by an increase in dosage to 500 mg. daily. Wadell [8] found a similar secondary rise. The cholesterol levels were unaffected by triparanol in 3 of his 12 treated patients. In 6 of the 9 who responded initially, the cholesterol had returned to the control value after four months' treatment.

The clinical value of triparanol in the treatment of arterial disease is still undecided. It will often produce a moderate fall in blood-cholesterol, especially if the initial level is high; but in place of cholesterol, desmosterol accumulates, and this may well be as atherogenic as cholesterol. The lowering of cholesterol may persist for only a few months, though an increase of dosage may control this secondary rise.

DRUG DOSAGE FOR INFANTS

THERE is still no unanimity as to the best method of calculating drug dosages for infants and children. Eponymous rules [9 10] based on the age of the child (in years) include the following:

Cowling.—Average dose $\times \frac{\text{age}}{24}$

Young.—Average dose $\times \frac{\text{age}}{\text{age} + 12}$

Dilling.—Adult dose $\times \frac{\text{age}}{20}$

Bastedo.—Adult dose $\times \frac{\text{age} + 3}{30}$

Fried's Rule for infant dosage is:

$$\text{average adult dose} \times \frac{\text{age in months}}{150}$$

Another method, which relies on the weight of the child, is that of Clark:

$$\text{average dose} \times \frac{\text{weight in pounds}}{150}$$

Butler and Richie [11] make a plea for the adoption of calculations based on the surface area of the infant. This method is not new, but, though generally regarded as that which best defines the needs of infants and children, it is not widely used. The surface-area approximates to weight (kg.)$^{0.7}$—i.e., two-thirds power—with a standard deviation of 8%.

Butler and Richie found impressive differences in the doses of acetylsalicylic acid used in North American clinics, with a range of from 200 mg. to 60 mg. per kg. body-weight. They considered that dosage adjustments for sulphadiazine, digitoxin, and diphenylhydantoin were often inadequate; and that this was true also of the estimation of protein, caloric, and fluid requirements. They suggest that the determination of dosage according to surface area, or weight $^{0.7}$, is both convenient and accurate.

7. Kountz, W. B. *Progr. Cardiovasc. Dis.* 1960, **2**, 541.
8. Wadell, W. R. *ibid.* p. 597.
9. Grollman, A. Pharmacology and Therapeutics. London, 1958.
10. Lynn, E. V. Pharmaceutical Therapeutics. London, 1929.
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DOES BUERGER'S DISEASE EXIST?

IN 1879 von Winiwarter [1] published his pathological findings on the vessels of a leg amputated from a male patient; and almost thirty years later Leo Buerger,[2] impressed by the occurrence of limb gangrene in young men, attempted to define the histological and clinical characteristics. Since then Buerger's disease has been widely accepted as a distinct entity, although from time to time critical voices have been raised. From the clinician's viewpoint the disease is typified by thrombotic lesions, usually in small arteries but often involving veins, from the size of the tibials downwards, in men below the age of 35. The condition runs an episodic course with intervals of freedom during which a fine but rich anastomotic network is developed. The digital arteries are particularly liable to occlusion, in the hand as well as the foot; and in about a third of cases a segmental phlebitis, especially in the superficial veins, complicates the disease. As the disease progresses the resultant ischæmia may necessitate amputation of one or more limbs. Less commonly the thrombotic lesions may be localised to the popliteal artery with a normal arteriographic picture above and below the block: yet, in many such cases, on follow-up the small-vessel disease attributed to thromboangiitis obliterans will have developed.

The histological basis for diagnosis is even less secure: "there is so much variation from case to case, depending upon the stage of the disease and the characteristic capriciousness of the lesions, that it is difficult to give a succinct account of the histology . . ." [3] How much the classical three phases of acute arteritis, organising thrombus, and recanalisation depend, not on a specific ætiological factor, but on the cellular reactivity of small-calibre vessels in a young man is debatable.

Wessler et al.[4] now argue against regarding Buerger's disease as a separate entity. They point out that in vascular clinics the frequency of the diagnosis has greatly declined over the years; and in the past eleven years at the Beth Israel Hospital no new cases of Buerger's disease have been recorded despite a sharp rise in cases of arterial obstruction due to other causes. They have reviewed retrospectively 84 cases in which arterial disease of the legs developed before the age of 45. In 36 of these, heart-disease or gross atherosclerosis were present; and in this group—presumably all atherosclerotic—phlebitis was present in 62%, compared with 41% in the remainder. 35 amputations from 18 patients were available for examination. In 10 atherosclerosis was present, and in 3 systemic arterial emboli; in the remaining 5 the morphological nature of the occlusion could not be determined. It was not uncommon to find organised thrombosis without atherosclerosis in a distal artery, whereas in the proximal artery of the same limb atheromatous narrowing was evident. Section through the "normal" vessel revealed, therefore, a histological picture not unlike that said to be found in Buerger's disease. The histological data from superficial-vein biopsy were

1. von Winiwarter, F. *Arch. klin. Chir.* 1879, **23**, 202.
2. Buerger, L. *Amer. J. med. Sci.* 1908, **136**, 567.
3. Dible, J. H. *in* Peripheral Vascular Disorders (edited by P. Martin, R. B. Lynn, J. H. Dible, and I. Aird). Edinburgh, 1956.
4. Wessler, S., Si-Chun Ming, Gurewich, V., Freiman, D. G. *New Engl. J. Med.* 1960, **262**, 1129.

similarly unrewarding, and the inflammatory changes probably did not differ from those to be expected in, say, thrombosed varicose veins. Wessler et al. conclude that there is no specific histological picture characteristic of Buerger's disease, either in the arteries or in the veins, and that the condition described by Buerger is indistinguishable from atherosclerosis, systemic embolisation, or bland thrombosis in a reactive vascular system. They suggest that Buerger never presented data (and they are highly critical of his reproduced histological pictures) sufficient to define a distinct morbid process, and they recommend that the term be discarded.

Most clinicians and pathologists will agree in general with these conclusions: Buerger's disease is doubtless wrongly and excessively diagnosed. The clinician is overimpressed by the youth and sex of the patient, and the pathologist—often limited to a vessel far from the seat of the main lesion—finds a relatively normal appearance, either with an organising thrombus or with a mild inflammatory reaction, and concurs with the suggested diagnosis. Digital-artery lesions, as distinct from major arterial thromboses, are common in elderly women; but because of the age and sex we do not term these Buerger's disease: phlebitis is frequently present in the history of the elderly atherosclerotic but does not influence the diagnosis. It is time we escaped from the idea that limb atheroma does not develop in young men; doubtless most cases of so-called Buerger's disease are due to atherosclerosis in small reactive vessels, and follow-up shows that a notable proportion die of clearly atheromatous coronary-artery disease. But can we discard altogether the concept of thromboangiitis obliterans?

ROLV GJESSING

IN an annotation on depression last week we referred to a " crucial observation " by Gjessing.

The death of this investigator in March of last year at the age of 72 ended a remarkable medical life.

The son of a Norwegian minister, he worked first, for seven years, as a practitioner and Government medical officer in a post beyond the Arctic circle. His anthropological observations among the Lapps were later published in a monograph. Beginning to specialise in psychiatry, he travelled widely and spent six months in the United States, where focal infection in mental patients was then being investigated. The Rockefeller Foundation helped him to equip the laboratories which he had started and organised at his own expense; and within fifteen years Dikemark Mental Hospital outside Oslo became a centre of research in the metabolism of psychosis, especially of periodic catatonia.

Gjessing recognised the importance of recurrent psychotic attacks of a definite duration, separated by free intervals, for the investigation of physical changes. In a special unit, clinical and laboratory methods could be applied to a small number of suitable patients—e.g., intake and output, regular tests of the blood and intermediary metabolism, movements, and energy balance. By his understanding approach, Gjessing made the patients themselves his most careful and devoted collaborators, and his unit became a model for other metabolic units all over the world. His wise insistence on following up a small number of well-characterised psychotics over a considerable time, comparing their conditions in excitation or stupor with the symptom-free remission, enabled him to recognise changes in the protein metabolism and nitrogen balance which he was able to correlate with disturbances in the vegetative nervous system and the patients' behaviour. Subsequently he came to the conclusion that physical as well as psychological manifestations could be improved by stimulation of thyroid function: thyroxine, thyroid extract, and thyrotropic hormone can, if properly applied, suppress the recurrence of psychotic attacks. After his retirement, he was invited by A. B. Stokes to be visiting professor at Toronto University and to continue his studies of periodic psychoses.

Gjessing's investigations, minute in details and comprehensive in their planning and execution, are almost all published in German.[1] This and his opposition to the empiricism of much contemporary psychiatric treatment may explain the small resonance he has found so far in English-speaking countries.

NOBEL PRIZEWINNERS

THE 1960 Nobel prize in medicine has been awarded to two men who are widely regarded as the outstanding British biologists of the day—Sir Macfarlane Burnet, O.M., F.R.S., director of the Walter and Eliza Hall Institute of Medical Research in Melbourne, and Prof. P. B. Medawar, F.R.S., Jodrell professor of zoology and comparative medicine at University College. The award is made for their discovery of acquired immunological tolerance, described as one of the greatest events in the history of immunology and the starting-point of a new era in experimental biology.

The discovery stemmed from Burnet's idea of the " self-marker "—that cells " learn " to distinguish their own proteins from foreign proteins, and produce antibody to foreign proteins but not to their own. Since embryonic cells do not produce antibody, Burnet suggested that this hypothesis could be tested by " deceiving " the cells. To do this, a foreign protein had to be injected into the embryo early in its development; and then, according to the hypothesis, the protein might subsequently behave like one of the embryo's own proteins, so that in the adult animal injections of the foreign protein would not evoke the production of antibody. At first, the experiments gave negative results, but some years after the theory was published Medawar and his colleagues carried out elegant experiments which gave just the expected results. They found that mice injected during embryonic life with cells from a foreign strain of mice were able, in adult life, to tolerate grafts of skin from the foreign mice. This acquired immunological tolerance has now been demonstrated for many different antigens, and the elaboration of these findings has meant radical revisions in immunological theory.

Burnet is similarly renowned for his researches on viruses and for his wide ranging, at both experimental and theoretical levels, in the whole territory of biology. Medawar has also made a notable contribution by his demonstration that the rejection of skin homografts is an immunological reaction; and recently the Medical Research Council announced his appointment, from 1962, as director of the National Institute for Medical Research.

Sir CLEMENT PRICE THOMAS has been elected president of the Medical Protection Society.

The next session of the General Medical Council will open on Tuesday, Nov. 22, at 2.15 P.M., when Sir DAVID CAMPBELL, the president, will deliver an address. The Medical Disciplinary Committee will sit on Wednesday, Nov. 23, at 10.30 A.M.

1. Disturbances of Somatic Functions in Catatonia with Periodic Course *J. ment. Sci.* 1938, **84**, 608. Beiträge zur Kenntnis der Pathophysiologie des katatonen Stupors, *Arch. Psychiat. Nervenkr.* 1932, **96**, 319, 392; 1935, **104**, 355; 1939, **109**, 525. Report on 8th Congress of Scandinavian Psychiatrists, *Acta psychiat., Kbh.* 1947, p. 93. Beiträge zur Somatologie der periodischen Katatonie, *Arch. Psychiat. Nervenkr.* 1953, **191**, 191, 220, 247, 297; 1960, **200**, 350, 366.

Public Health

Q FEVER IN NAVAL PERSONNEL

P. K. FRASER
M.D. Glasg.
SURGEON CAPTAIN, R.N.
L. A. HATCH
M.B. Lond., Dip. Bact.
R. J. CARMICHAEL
M.B. Lond.
SURGEON LIEUTENANT, R.N.
A. D. EVANS
M.B., B.Sc. Wales, Dip. Bact.
With the technical assistance of
J. M. R. FORSTER, F.I.M.L.T., *and* J. E. GOODINGS, A.I.M.L.T.
From the Department of Pathology, Royal Naval Hospital, Haslar, H.M.S. Royal Arthur, *the Public Health Laboratory, Portsmouth, and the Public Health Laboratory, Cardiff*

Q FEVER has been recognised in this country since 1949. Laboratory investigations have revealed sporadic cases and small localised outbreaks. The disease is characterised by an acute pyrexial illness with severe headache, cough, and signs of pneumonia. Convalescence is usually uneventful, and the case-fatality rate is low. Occasionally chronic infection occurs (Evans et al. 1959, Robson and Shimmin 1959).

The present investigation was prompted by the admission of a case to this hospital in July, 1959.

The patient, a man of 41, had a history of cough, shivering, and sweating for three days. He had no headache. Radiographs of the chest showed bilateral basal bronchopneumonia. The leucocyte count was 6500 per c.mm. and the erythrocyte-sedimentation rate (Wintrobe) was 39 mm. in the first hour. Serological evidence of infection with *Rickettsia burneti* was obtained; complement-fixation tests on sera taken seven and nineteen days after the onset of illness showed titres of less than 1 : 5 and 1 : 320 respectively.

The patient had returned from a training course in Wiltshire and the Black Mountains of South Wales on July 16. It was obviously possible that other men who attended this course had also been infected, and special investigations into this unit gave the following information.

Investigations

The index case joined class 645 at a Naval establishment in Wiltshire on June 4, 1959, and was on training in the Welsh mountains in the first week in July. Since the investigation did not begin until late August only single sera were obtained from men who attended the course in the early summer. From later courses it was possible to obtain sera from men on joining and leaving the courses and again three weeks or more later.

All sera were tested in a complement-fixation test using seventy-five minutes' fixation at 37°C and antigens of seven upper respiratory viruses as previously described (Fraser and Hatch 1959). A titre of 1 in 10 or greater against *R. burneti* in the human sera was considered suggestive of recent exposure.

In addition, sera from cows and sheep in the vicinity of the farm buildings used as a base in the mountains were tested against *R. burneti*.

Specimens for attempted isolation of *R. burneti* were extracted with sterile saline and inoculated into guinea-pigs in two laboratories independently. These animals were killed six weeks later and their sera tested for complement-fixing antibodies to *R. burneti*.

Findings

Each week a group of about 25 men joined an establishment in Wiltshire. After five weeks they went by road to the Black Mountains in Breconshire, where they stayed for three days before returning to Wiltshire and dispersing to other Naval units. In the mountains they used as a base a ruined farmhouse with attached farm buildings set high on the side of a valley, but walked over the mountains in groups of three to test their ability to operate in open country. They lived in the open for about thirty-six hours during this test. Sheep and cattle sheltered in the farm buildings and grazed the surrounding pastureland. Lambing and calving occurred here during the winter and spring. The products of parturition were said to have been either buried or eaten by the animals and no traces could be found. Rat infestation was noticed, but it was not considered to be heavy. Contact with these animals and their excreta during the stay was inevitable. In addition men from some groups complained of multiple insect bites mainly on the head, neck, and forearms.

618 men underwent the course between May 7 and Nov. 12. They were in the mountains between June 13 and Nov. 10.

372 men were in classes 640–653, which were in the mountains between June 13 and Sept. 8. Sera were obtained from 368 of them at times varying from three weeks to four months after leaving the training area, and table I shows their distribution of antibody titres to *R. burneti*.

There were 64 men in classes 654–656. They were in the mountains between Sept. 12 and Oct. 24. All were serologically negative four days after leaving the mountains. 62 were examined again one month or more later. 1 man in class 654 had a rise in titre to 1 in 80, and another in class 656 had a titre of 1 in 10.

In classes 657–663, which followed, there were 182 men. All were bled on joining and leaving the training unit in Wiltshire and all were negative, although 1 man had unchanging titres of 1 in 10 in both sera and is not included in the totals. Further sera were obtained from 177 of them one month or more later, when 1 had gained a titre of 1 in 10.

Sera were tested from 83 members of the staff of the training centre in November. 2 had a titre of 1 in 10, another had a titre of 1 in 40. This last man had been in the mountains frequently and had had an influenza-like illness in August. The other 2 had not been in the

TABLE I—DISTRIBUTION OF ANTIBODY TITRES IN SINGLE SERA OBTAINED FROM MEN THREE WEEKS OR MORE AFTER LEAVING TRAINING CENTRE

Class no.	Period at training centre (1959)	< 1/10	1/10	1/16	1/20	1/40	1/80	1/160	1/320	No. in class	No. tested	No. positive
640	May 7 to June 18	30	..	..	..	..	..	..	..	31	30	0
641, 642	May 14 to June 25	38	1	..	..	..	1	..	..	40	40	2 (5%)
643	May 21 to July 2	27	1	..	1	..	..	..	..	30	29	2 (7%)
644	May 28 to July 9	28	..	..	..	..	..	..	..	29	28	0
645	June 4 to July 16	11	3	2	..	3	3	3	3	28	28	17 (61%)
646	June 11 to July 23	17	2	..	3	4	4	1	1	32	32	15 (47%)
647	June 18 to July 30	26	..	..	1	1	1	..	1	30	29	4 (14%)
648	June 25 to Aug. 6	24	..	..	..	1	2	..	..	27	27	3 (11%)
649, 650	July 2 to Aug. 27	45	..	2	1	1	2	..	..	51	51	6 (12%)
651	July 9 to Sept. 3	25	..	..	1	..	..	1	..	27	27	2 (7%)
652, 653	July 16 to Sept. 10	47	..	..	..	..	..	..	..	47	47	0

TABLE II—DISTRIBUTION OF ANTIBODY CHANGES IN 50 SEROLOGICALLY POSITIVE CASES TESTED THREE MONTHS AFTER DIAGNOSIS

Unchanged	2-fold fall	4-fold fall	8-fold or greater fall	2-fold rise	4-fold rise	Total
11	19	9	8	2	1	50

mountains but handled bedding and clothing returning from Wales.

There were 57 serologically positive cases in all. Of the 55 men who had been to the mountains, 39 had had no illness after they had left. The other 18 (36%) were ill within two weeks of leaving the centre—i.e., within about sixteen days of leaving the mountains. 2 had pneumonia; 1 had jaundice with high fever; and 15 had an influenza-like illness with fever, cough, headache, shivering, sweating, and general malaise. Radiological examinations of the chests of 53 of these men, two weeks after diagnosis, were negative.

Further specimens of serum were examined from 50 of the positive cases about three months after the initial diagnosis had been made. Table II shows the distribution of the changes in antibody titres in these men. 10 men had no detectable antibody in the follow-up specimen of serum; in 1 the titre had fallen from 1 in 320 to zero, and in 9 from 1 in 80 or less to zero.

No evidence of *R. burneti* was found in samples of dust taken by vacuum cleaner from clothing and bedding or in samples of litter from the farm buildings. None of the animals tested had antibody to *R. burneti*.

Discussion

Since the recognition of Q fever in this country (Stoker 1949, MacCallum et al. 1949), small outbreaks have been reported from most parts of England and Wales (Marmion and Stoker 1958). As might be expected in a disease normally affecting cattle and sheep, most cases have occurred in persons in contact with these animals.

It has been shown that about 5% of the herds of cattle and about 3% of the flocks of sheep in South Wales are infected, but only about 0·6% of the cases of abacterial pneumonia in the area are due to Q fever (Evans 1956).

Q fever was of considerable military importance in Italy from 1943–45. Robbins et al. (1946) investigated an outbreak there and found that 269 of a battalion of 900 men were admitted to hospital from this cause in one three-week period.

Since the present investigation began several weeks after the peak incidence of infections, some of the positive titres which were found may have been present before the men joined the training centre. However, of 182 men examined on joining the centre after the peak incidence, only 1 had a titre of 1 in 10 or greater. During 1958 and 1959, of 1323 patients with upper respiratory infections who were admitted to this hospital, and over 2000 recruits from all over this country, considerably less than 1% had demonstrable antibody to *R. burneti*. There was no evidence of an increase in the number of the civil and Naval populations in South Hampshire who had antibody to *R. burneti* during the period of investigation, yet in many of the positive cases the men had been sent on the course from ships and establishments in this area.

R. burneti was not found in dust obtained from the men's clothing or the litter in the barns in Wales. Inspection of the premises showed that men living in the farm-house must have been exposed to large quantities of dusty litter which was heavily contaminated with animal excreta. In addition the cattle and sheep which were known to have used these barns and to have been in contact with the men were shown to be free from Q fever.

The men walked over country grazed by flocks of sheep which were known to have been infected in previous years. The men travelled along sheep tracks on the limestone or sandstone hillsides, which were contaminated with animal excreta. Since there was no rain in the area from about the middle of May to the beginning of August, these tracks were dusty. Inhalation of some of this potentially infected dust was inevitable, particularly during rest periods when the men were sitting or lying down.

Lambing in the area was almost completed by April, but a few lambs were born in May. Although no products of parturition were seen by the class leaders who were in the area in June and July, it is possible that, because of the dry weather, dust derived from the afterbirths of late-lambing ewes could have caused infection in the men.

On the other hand it is difficult to account on this basis for the large increase in cases in the latter half of July. It seems more likely that one or more new factors developed, or an existing factor increased, temporarily during this period. There is no evidence to clarify this point other than the history of numerous insect bites sustained by the men during this period.

The evidence suggests that most of the infections occurred in the latter half of July, probably in the Black Mountains; but the method of infection has not been demonstrated. The men were dispersed two to three days after the course and there was no evidence of further outbreaks, although 1 further case of Q fever occurred in each of 2 establishments to which a patient returned; these further patients had not undergone the course.

Since ticks were not seen, and the men wore boots, gaiters, and denim trousers during training, ticks were probably not the vector.

It is unlikely that these men developed chronic rickettsæmia, since at examination some three months after infection they were well and in most instances their titres to *R. burneti* had fallen. About two-thirds had diminished antibody titres; about a quarter had unchanged titres; and 3 (6%) had slight rises in titre. 16 of 18 clinically positive cases had antibody three months after the illness.

There is a similarity between these findings and those of Holland et al. (1960), who investigated Q fever in R.A.F. personnel. Since in each of the two series the proportion of asymptomatic serologically positive cases was high, the possibility exists of case-to-case spread between men in close contact with each other under field conditions. In view of the findings of Evans and Baird (1959) the history of insect bites may have some significance, but there is insufficient evidence to determine their role in this outbreak.

Summary

A patient admitted to hospital in July, 1959, was found to have Q fever. Studies on 618 Naval personnel from a training course in Wiltshire and South Wales which this patient had attended showed that 54 men had antibody to *R. burneti* and that over half of 28 men in his particular class had been infected. 3 additional cases were also detected in the staff of the training base.

Most of the infections occurred in the last two weeks of July. The evidence suggests that infection took place in the Black Mountains of Breconshire, but the mode of infection was not found.

Examination of 50 men three months after diagnosis showed no evidence of chronic rickettsæmia, although 3 had slight increase of antibody to *R. burneti*.

We thank the Medical Director General of the Navy for permission to publish; Prof. A. Bradford Hill for statistical advice; Surgeon Rear Admiral G. Phillips and Dr. K. E. A. Hughes, director, Public Health Laboratory, Portsmouth, for their advice and encouragement throughout; the medical officers of the Royal Navy for their assistance in supplying information and serum samples without which this investigation would have been impossible; Dr. P. V. Pritchard, medical officer of health for Gosport, for his interest in the index case; Surgeon Captain J. H. Nicolson, R.N., who afforded us all facilities in his area; the medical officers of health and the directors of the Public Health Laboratories in the areas concerned for their cooperation; and Mr. E. H. O'Connor, A.I.M.L.T., for his technical assistance.

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The Widdicombe File

LXV.—"PLUCKED FROM THE BURNING"

DEAR WHIDDON,

Jan wanted me to slip over and see his son at Witherbridge. As you'll know, he's out of danger now. I suppose a fractured femur, ruptured gut, and a few burns are not really a very high price to pay for wrapping that sports car round a tree at 85 m.p.h. Thank God nobody was in the way. The local boys did a wonderful job; they're slick on accidents and my second opinion couldn't add much.

Jim was certainly lucky in choosing his spot, for the chaps at Witherbridge had him transfused and on the table within an hour. I reckon that if his track-rod had chosen to snap half an hour before it did, there would have been a good three-quarter-hour journey by the Milvercombe ambulance, with a ten-minute delay on Suffering Hill where the road's up, plus any amount of time in getting to the telephone in the first place. St. Ethelred's is quite good of its sort, but the casualty officer hasn't had much experience and finds conversation difficult except in Tamil; though they're lucky to have him, for the job was unfilled for a couple of months.

If Jim had arrived there, a cubicle would have been quickly cleared of a patient with multiple boils and another with athlete's foot; and those two old porters would have done their best to heave him off the stretcher on to a couch. It's usually possible to trace the Egyptian R.S.O. within 20 minutes (there's still no call-system you know) but he wouldn't have been able to do much except call the surgeon from one of the other hospitals and order blood. The consultant, when he got away from the advanced carcinoma he was trying to remove, would have found shifting dullness and things and ordered immediate operation, though being a general man he wouldn't have liked plating that femur. Still, Sister would take about half an hour to get the theatre ready, and by then maybe an orthopod could have been found. The moves from couch to trolley and trolley to operating-table wouldn't have helped, not to mention the trip down to X-ray, a couple of hundred yards away.

Jim needed arterial transfusion with assisted respiration and quite a lot of tissue grafting, which called for resources and personnel of a very high order. St. Ethelred's, I'm afraid, has neither. So I might easily have been writing a letter of condolence, instead of this fairly cheerful one to you. (So I might, in point of fact, if he'd been brought to my own hospital.)

Would it help, do you think, if we started calling the motor-car Captain of the Men of Death? Both the Industry and the Government seem *incredibly* oblivious of the enormous suffering that surrounds us. If anyone were seriously interested in prevention, then safety-design in roads and cars, an overall speed-limit, and a ban on high-powered motor-bikes for youngsters seem obvious; and then there's liquor, and why not make seat-harness compulsory on Motorways? Punishment for the delinquent driver should become realistic, and not just the present meaningless penny-penances and vague warnings.

Still, some accidents are bound to happen, even if we return to stage-coaches. What do you think we ought to be doing on the medical side to halt the rising tide of death and disablement? What, for that matter, is your own ex-teaching hospital saying or doing? Some have whole-time accident surgeons on a 24-hour service, though mine, I regret to admit, has *no* consultants working no time; and lots of departments are manned at night only by a reluctant H.S. or H.P., heavy-lidded from a hard day's work. Obviously we can't have the Witherbridge sort of accident team in every hospital, but we could have more of them. Some people want 25 or so centres to cover the whole country, and it sounds sense to me, though probably far too few. Probably you have views on staffing; but I hope you'll agree anyway that the centres need to be specially designed, in or near a large and efficient general hospital with ambulances (and helicopters?) going straight to them.

All this seems so obvious and desirable and important that I suppose it's quite impossible; and that's what it does in fact seem to be when one puts it to one's colleagues. "What, close our Casualty?" they say; "what a blow to our prestige. G.P.s won't send us cases, and how will Matron train the nurses?" General and orthopædic surgeons get at each other's throats, and the whole affair gets bogged down in petty politics and silly jealousies. I suppose it's hard to expect cooperation between adjoining hospitals whose senior staff haven't recognised each other's existence since 1893. But eventually, if we don't do something effective, the Ministry will decree a Central Plan of some kind—and not before time perhaps. We all know now—thanks to the independent Nuffield set-up—just how bad some old casualty departments are and how little thought sometimes goes into the planning even of new ones. No doubt you know, too, that a confusion of committees has been set up to look into this and that. Make life safer for Jim's children maybe. But the best hope (as I think has happened in two, or perhaps three regions) is for the local men themselves, and the S.A.M.O., to take a long hard look around.

Accident surgery has been remarkably neglected compared with things like plastics and chests, though the people it works on could hardly be of greater value to society. It's funny, too, that most of the chaps who are trying to do something about it seem to be near-descendants of those Colonial pioneers who lately made our great Dominions what they are. Maybe it takes an outsider to see where we fall short.

As ever,

P.G.

Conferences

GREAT ISSUES OF CONSCIENCE IN MODERN MEDICINE

FROM A CORRESPONDENT

Dartmouth College in New Hampshire, which boasts the third oldest medical school to be in continuous operation in the United States, staged a convocation on this topic on Sept. 8–10. To discuss these issues the following were asked:

René Dubos, bacteriologist and member of the Rockefeller Institute; Mahomedali Currim Chagla, laywer, India's Ambassador to the United States and Mexico; Brock Chisholm, Canadian physician, director-general of the World Health Organisation from 1948 to 1953; Ward Darley, executive director of the Association of American Colleges; Ralph Gerard, director of laboratories at the Mental Health Research Institute, University of Michigan; Aldous Huxley, novelist and essayist; George Kistiakowsky, Harvard professor and special assistant to President Eisenhower for science and technology; J. H. Muller, Indiana University, Nobel laureate for his work on genetics; Walsh McDermott, professor of public health, Cornell University; Wilder Penfield, director, Montreal Neurological Institute; Sir George Pickering, regius professor of medicine, Oxford University; Sandor Rado, dean and professor of psychiatry, New York School of Psychiatry; Sir Charles Snow, physicist and novelist; and Warren Weaver, vice-president of the Sloan Foundation and former vice-president of the Rockefeller Foundation.

Pollution

Dr. DUBOS pointed out that science is not concerned with moral or ethical issues. It teaches how to do, not what to do. In general it is society at large that decides what to do. Dubos recalled that Hermann Biggs, a former commissioner of health for New York State, had written: "Public Health is purchasable. Within natural limitations any community can determine its own death-rate." He said:

"The origin of the most important air pollutants is well known. Depending upon the locality, they comprise: the products arising from incomplete combustion of organic matter; the various chemicals released from the smokestacks of industry; the exhausts of motor-cars; the catalytic oxidising effect of solar radiation on nitrogen oxide and olefins; and mixtures of all these factors. Without the need of any further investigation, it is clear that certain courses of action would go far toward minimising the medical problem caused by air pollution. To improve the design of combustion equipment and of gasoline engines, to increase the height of smokestacks, to re-route automobile traffic, to displace certain industries, &c., are steps compatible with technical knowledge and which would either eliminate air pollutants or discharge them in areas where they would not constitute threats to human health. But these steps could be taken only at the cost of disturbing the economic structure of the community, and of creating inconveniences for almost every one of its members.

"In reality, then, the problem of air-pollution control is not only scientific in nature, but even more one to be formulated on the basis of certain human values difficult to express in terms of factual information. How much of economic prosperity and of convenience of life is society willing to sacrifice to prevent lung cancers, emphysema, and chronic bronchitis that will become apparent only in the future? How can we balance the value of human suffering that will occur in some undetermined future against the effectiveness of the social performance of a community today?"

MCDERMOTT told the story of the guest in the country house who, having asked his hosts what they did with garbage, received the reply, "Oh, we just kick it around till it gets lost." He thought our attitude to air pollution had been the same, and in fairness to our children we must now tackle it seriously.

Perhaps the most serious pollution problem is that of radioactive material, which, as DUBOS said, must always be a hazard, particularly to the workers, if atomic energy is to be used for peaceful purposes. PICKERING remarked that contamination through tests of atomic weapons was not the really serious issue, since these tests were deliberately performed in centres of minimal population density. What was serious was what lay behind them. Natural defence was, of course, two-sided. It should be plainly stated that war was the greatest threat to mankind, and that war was the most devastating disease the world was ever likely to know.

Man's Biological Future

The future course of world population and its social and political consequences were considered by the Indian Ambassador and Aldous Huxley. The AMBASSADOR made a moving speech dealing with the serious situation developing in India and appealing for help not in wealth but in "know-how". Here are some extracts:

"The great crisis of this decade is not one of differing ideologies. The great enemy and the threatening menace that we have to face is not Communism. The really explosive factor is poverty.

"At one time a rising population did not present a serious problem to India. There were always epidemics, or local wars, or a heavy infant mortality and a low expectancy of life to counterbalance the large number of births. I may also point out that people in those days looked upon a large number of children as an insurance—so few survived that a large family seemed to be essential. But all that has changed now. Advance in medical knowledge, steps taken to improve standards of hygiene, have eliminated many diseases in India which took a heavy toll of lives. There are no epidemics now, and if one breaks out it can be immediately put down. Civilisation no longer believes in small local wars—we have to wait for a nuclear holocaust. The result has been a sharp fall in the death-rate. But the birth-rate has remained the same. So in a sense we have been suffering from the civilising effects of science and medical research. Civilisation has shown us how to reduce our death-rate but so far has failed to point the way to a controlled population. I think this is one of the most important issues of conscience in modern medicine. Medicine must advance on both the fronts. If it considers life is sacred and everything must be done to prolong it, it must also prevent human beings being born into an existence of poverty, destitution, and frustration. The sanctity of life demands that the dignity of the individual must be upheld. What dignity will millions of children have who are being born today?"

"I should like to say a word about the ethical or moral aspects of the problem. To my mind morality consists in giving the least pain to fellow human beings and contributing to the largest extent to their well-being. This is not, I fully appreciate, a philosophic definition of morality. But it is a pragmatic one and can serve as as good a guide to human conduct as any other. Applying this test, I think you are causing more misery and suffering to untold millions by denying a knowledge of birth-control technique than by doing everything possible to bring home to the people in this country the vital urgency of the problem of population explosion that is facing the world. Nor am I impressed by the argument that it is morally wrong to take life—that we should trust to a benign and benevolent providence to feed all the mouths that exist in this world. Experience, unfortunately, does not prove that all mouths are

in fact fed. Millions in Asia and Africa go hungry and underfed. I would rather prevent life than bring into existence children who do not and cannot live as human beings and who are a shame and a scandal both to providence and to man."

"You might well ask me what India herself has done toward the solution of this tremendous problem that faces her. We are one of the very few Governments in the world who have officially adopted a policy of birth-control and family planning. It is not easy for any Government to do this. There are orthodox people in every religion who are opposed in principle, whatever the principle may be, to birth-control. Religions in India are no exception to this. But our Government has placed the welfare of its people before religious sentiments, and, even at the risk of offending these, has set up clinics in various parts of India to propagate extensive knowledge about birth-control and distribute contraceptives free of any cost. We have about 1800 such clinics now and by the end of our next five-year plan—in five years' time—we hope to have about 8200. I agree that this is merely the fringe of the problem."

This speech deeply impressed the meeting, as did that of ALDOUS HUXLEY, who asked what were the humane and natural substitutes for Nature's method of dealing with over-population—namely, famine, pestilence, and, in human societies, war. First, we can increase production of food and industrial goods. This is feasible, but in the long run increase of population if unchecked will outrun increase in production. Thus when the high dam at Aswan is completed the population of Egypt will have increased to a point where the newly irrigated land will not suffice to feed it. Consequently efforts to increase production must go hand-in-hand with efforts to bring birth-rates into balance with death-rates. Unfortunately death control is easy and cheap, birth-control is expensive and difficult. Though a rational population policy, internationally agreed upon, would not bring an immediate solution to our problems, it must nevertheless be adopted. If it is not, our grandchildren and greatgrandchildren will be in for the worst time of trouble ever faced by the human race. Increasing quantity will result in deteriorating quality of living, and most of the world will sink into abysmal squalor and chronic warfare.

Perhaps the most astonishing feature of the convocation was the fierce disagreement with these views expressed by MCDERMOTT and DUBOS. Both doubted whether medical science had had much to do with increasing world population or whether this would be a serious problem. MCDERMOTT thought ancient Rome was probably as sanitary as modern Calcutta. DUBOS, after Chagla and Huxley had spoken, thought it significant that the two experts on infectious diseases should be in opposition to the rest of the group. To your reviewer it seems astonishing and rather tragic that scientists can be so prejudiced. Has modern medical science been entirely without influence on such great epidemic diseases of the past as malaria, typhus, plague, and smallpox?

Other Topics

The remaining issues produced neither such highlights nor such controversy. The problem of the extent to which doctors should go to keep senile or suffering patients alive was raised but not fully discussed. It was agreed that, if society wants euthanasia, it should not ask doctors to carry out its instructions but should license people specially for the purpose.

The extent to which we should try to improve the quality of mankind by employing genetic knowledge and the practices so successfully used in breeding cattle and racehorses received no satisfactory answer. MULLER thought that, to prevent the serious genetic conseqences of radiation, all men at present living might have their sperm stored in refrigerated underground tanks. DUBOS thought this was perhaps the oddest legacy one generation could leave to the next.

The session on factors influencing the mind dealt largely with brain-mind relationships and with current views of the nature of conscience. The psychiatrists agreed that unrestricted permissiveness was unjustifiable and was now "out". The practice of "brain washing" was unfortunately not discussed.

Your correspondent and the two thousand others attending the convocation undoubtedly found it stimulating. Though no issues of conscience were settled, they became more sharply defined.

GASTRIC SECRETION

FROM A CORRESPONDENT

ON Oct. 15 a symposium on Gastric Secretion was held at the Western General Hospital, Edinburgh, under the auspices of the Postgraduate Board for Medicine. The participants included representatives of the disciplines of anatomy, physiology, pharmacology, endocrinology, medicine, and surgery.

G. M. WYBURN (Glasgow) discussed the structure of the parietal cell as seen with the electron microscope—a technique that brings almost a new dimension into our understanding. The day may not be too far distant when enzyme arrays become anatomical actualities.

The problem of determining from the composition of mixed gastric secretion its original constituents was discusssed by E. BLAIR and A. A. HARPER (Newcastle), J. N. HUNT (London), and A. H. JAMES (Cardiff). The assumptions that have to be made in such inference were clearly underlined and also the dangers in the extrapolation of data that is necessary. It is still uncertain that stimuli to the parietal cells to produce hydrocholoric acid always work through the intermediate release of histamine: H. M. ADAM and H. MAIN (Edinburgh) produced evidence further supporting this hypothesis, but in another communication H. M. ADAM and W. T. IRVINE (London) described their failure to detect any rise in histamine in the venous effluent from the dog's stomach following stimulation of secretion.

W. SIRCUS (Edinburgh) described the biphasic pattern of gastric secretion in dogs following the induction of hypoglycæmia, and summarised the results of experiments designed to elucidate these changes. A. W. KAY (Sheffield) discussed the possible explanations for the much lower response of the human stomach to injected histamine after vagotomy.

HILDA TRACY (Liverpool) discussed some of the properties of gastrin and the response to gastrin injections in a human subject.

R. A. GREGORY (Liverpool) reviewed enterogastrone as an inhibitor of gastric secretion. He concluded that fat in the duodenum acted by inhibiting the release of gastrin from the antrum.

The drama of the Zollinger-Ellison syndrome has excited the attention of clinicians and physiologists for some years, and B. G. ALTON (Dublin) described an admirably documented case which included a study of the effects of acid in the small intestine on fat absorption.

G. P. CREAN (Edinburgh) showed, in a careful study, the effect of hypophysectomy in reducing the parietal-cell populations of the rat's stomach; while R. B. WELBOURN (Belfast) produced evidence that the effect of cortisone in potentiating gastric secretory responses might be exerted through an increase in the number of secreting cells.

The ability of long-continued oral administration of an adrenal inhibitor to decrease gastric secretion in dogs was shown by A. P. M. FORREST (Glasgow).

The gastric secretion of blood-group substances and their quantitative measurement was described by D. A. PRICE EVANS (Liverpool); the mystery of their relation to the incidence of ulcer and indeed of the significance of their presence in the gastric juice remains unsolved.

D. H. FRIEDLANDER (Edinburgh) showed how the efficacy of antacid therapy could be related to the secretory capacity of the stomach.

Medicine and the Law

A Draft Suicide Bill

POSSIBLE changes in the law of suicide are foreshadowed by a report from the Criminal Law Revision Committee published last week.[1]

Throughout the centuries suicide in England (though not in Scotland) has been a criminal offence as well as an ecclesiastical sin. Attempted suicide has been recognised by the courts as a crime since 1845, although today the police prosecute only where there is some definite circumstance calling for punishment or where an order of the court seems the only chance of securing help for a person too weak to stand alone.[2] "A severe lecture on their stupidity is mostly delivered to the offenders by a senior officer who has already satisfied himself he can hand over their future well-being to relatives or friends willing to look after them."[3]

If suicide is an offence, it must also be an offence to aid or counsel anyone to commit or attempt suicide. Indeed, the English law is that the person who does so is punishable as an accessory to murder, except that in the case of suicide pacts the offence is reduced to manslaughter by the Homicide Act, 1957.

The Criminal Law Revision Committee was not asked to consider whether changes in the law would be desirable. It was told in November, 1959, that the Home Secretary was considering whether legislation should be introduced to provide that suicide and attempted suicide should no longer be criminal offences. The committee was asked to consider what consequential amendments in the criminal law would be necessary on the assumption that it should continue to be an offence to incite or assist another person to kill or attempt to kill himself.

The report is therefore entirely concerned with the legal problems which would be involved. The main proposal is for a new statutory offence of aiding, abetting, counselling, or procuring the suicide of another or an attempt by another to commit suicide; for this a maximum punishment of 14 years is proposed, the court being left free within this maximum to adjust the penalty to the circumstances of each case. This proposal is said to be broadly similar to suggestions put forward by the Criminal Code Bill Commission (1879), the Royal Commission on Capital Punishment (1953), and a committee of the Church Assembly Board for Social Responsibility (1959).

Included in the report is the draft of a Bill to abrogate the offences of suicide and attempted suicide, and to give effect to the committee's recommendations.

1. Criminal Law Revision Committee: second report (Suicide). H.M. Stationery Office. 9*d*.
2. Williams, G. The Sanctity of Life and the Criminal Law. London, 1958.
3. Wyles, L. A Woman at Scotland Yard. London, 1952. Cited by G. Williams (footnote 2).

It remains to be seen what changes would follow in the practice of coroners' courts. The verdict that the deceased committed suicide whilst the balance of his mind was disturbed was introduced to prevent legal consequences which have long since ceased to apply. But this form of verdict is still relevant for life-assurance policies and for the burial laws of the Church of England.

Court Orders Transfusion

SOME months ago the Sheffield Regional Hospital Board caused some controversy by announcing that it had set up machinery for dealing with cases where a parent refused permission for a blood-transfusion to a child; under these arrangements, the local magistrates would be called to the hospital and asked to make an order under the Children and Young Persons Act committing the child to the care of a fit person.[1]

At Cambridge last week the magistrates sat at a local maternity hospital to deal with the case of a newborn baby suffering apparently from a rhesus-negative condition. The father, a member of the Jehovah's Witnesses, had refused permission for a blood-transfusion on religious grounds. The court made an order committing the child to the care of officials of the county council's children's department, who authorised the operation. The chairman of the court said: "It is a magistrate's duty to protect the life of the child."[2] According to one press report, the operation was performed within an hour or so of the birth. It would seem therefore that the father's attitude was known and the arrangements for the court to meet were made before the birth.

This is apparently the first occasion on which this procedure has been used in order to secure legal authority for an operation in opposition to the parents' wishes. Since the risk of a prosecution for manslaughter has proved no deterrent in such cases,[3] it would seem right that some such legal procedure should be available where there is a clear risk to a child's life or health. But the Children and Young Persons Act was obviously intended for quite different circumstances, and there is some doubt as to whether it can lawfully be used for sanctioning medical or surgical treatment. The Cambridge authorities acted reasonably in the circumstances, but it would be preferable to have specific legislation for this type of case.

Death Associated with Thorotrast

AT an inquest in Manchester on Oct. 19, the city coroner, Mr. Donald Summerfield, recorded a verdict of death from war injuries on a 37-year-old man who had died in Manchester Royal Infirmary. It was stated that his skull was fractured in 1943 in an accident while he was serving in the Royal Tank Corps.

Dr. Alexander Nicol said in evidence that at that time 'Thorotrast' had been injected intravenously for radiographic examination, and, according to then-existing knowledge, it had been properly administered. At necropsy he found that œsophageal varices had caused fatal hæmorrhage, and that the condition had been set up by cirrhosis of the liver. "In the man's liver I found a deposit of the substance, and over the years it had led to the disease which resulted in his death." Dr. Nicol added that since 1950 it had been accepted that thorotrast could cause cirrhosis of the liver, and its use for X-ray purposes had been discontinued.

1. See *Lancet*, 1960, i, 687.
2. *Times*, Oct. 21, 1960; *East Anglian Times*, Oct. 21, 1960.
3. See *Lancet*, 1958, i, 583.

In England Now

A Running Commentary by Peripatetic Correspondents

IT seems to be about as difficult for a word to gain formal admission to the French language as it was, in Biblical times, for a rich man to enter the Kingdom of Heaven; it has to be put up for discussion, debated, defined, and distinguished from existing rivals under the august arbitration of the Académie française, and even after this ordeal some weeks or even months must elapse before its *réception solemnelle*. Needless to say, and most happily for the continued survival of the language, none of this has the slightest effect upon the usage of the word by the public or even, I dare say, by the members of the Académie themselves. The most unexpected words have a spontaneous vitality of their own.

Take, for instance, the Word of the Year, " cybernetics ". This must be one of the few really indispensable pieces of semantic equipment for the traveller abroad in 1960, and it has already entered into the French that Frenchmen speak. Readers of *Zazie dans le Métro* will recall that at one point Gabriel, the sweet-smelling male *danseuse de charme* who rashly takes temporary charge of the unspeakably precocious Zazie, telephones Charles at the *bistro*. Charles, glass in hand, is trying to persuade the barmaid Mado-petits-pieds to marry him when she answers the phone. He fights a superbly negative delaying action (all those who have experienced French bureaucracy will know exactly what I mean) until his beaujolais is finished and then, " arrachant l'appareil des mains de sa peut-être future, il profère ce mot cybernétique: Allô ".

You see? It has become a part of life.

* * *

I am not much of an archæologist, but each summer when we go to the Highlands I follow the advice of the guide-books and visit whatever may be worth seeing in the locality. This year we went for the first time to Knapdale, and found it delightful. We chose our caravan site, on grounds that were mainly scenic, on an old road that wound its way through birch woods by the sea. The first thing, as usual, was to find a good supply of water. I wandered off to a nearby glade, which proved to have a nice fresh stream. It also had a cave in the rocks, which I idly entered. To my astonishment, this turned out to be St. Columba's first chapel in Scotland—or so says local tradition, which has often been shown to be correct about such matters. This first cell, Columba believed, was out of sight of his beloved Ireland, thus fulfilling his vow of banishment. There is an altar, a pulpit, a holy-water pool, and on the wall of the cave there is imprinted a cross. The pulpit, of natural rock, is at the entrance to the cave but so related to the roof that the speaker's voice is thrown out into the glade. A second cave may have been a dormitory. A fascinating place in every way, with a distinctive atmosphere to it. Poor Columba —that man of many vicissitudes—must have been sad to discover, one clear day, that he could in fact see Ireland on the horizon, so that he had to move on to Oronsay and eventually to Iona.

The curious thing about all this is that I have found no mention of it in any guide-book: but an ounce of discovery is more exciting than a ton of directed sightseeing.

* * *

Our children's physician arrived unusually late for lunch, and remarkably contented with life. The morning had produced a clinical pearl, some rare syndrome with real honest-to-goodness physical signs that she could demonstrate to the students. It had made her day, shedding a glamour over an outpatient clinic normally recruited from the young owners of running noses and capricious appetites. We congratulated her and then asked each other to describe what transformed a routine session into a memorable one. What makes your day?

The radiologist admitted to an inordinate, if private, satisfaction when an X-ray revealed a lesion which had been unsuspected or overlooked by the clinicians. The pathologist enjoyed drawing blood (and marrow) from metaphorical stones. Our neurologist's cup of happiness overflows whenever he is able to establish an exact diagnosis; apparently this happens excessively rarely. The surgeon was spoiled for choice. All his performances were spectacular—we gathered that was the reason operations were done in theatres. But there were subtle joys—deftly setting a transfusion going into some secret, invisible, impalpable, fully-patented-in-all-major-countries venule at the base of the little toe, after the anæsthetist had ploughed up all the official veins. The anæsthetist said, somewhat bitterly, that the sight of a surgeon including his own little finger in a ligature, or his screams as he snipped off the tips of his glove in the course of some fancy piece of scissor-work, rendered an operating list more than tolerable.

And we know, too, what makes a child psychiatrist's day. He told us, when he had worked his way through the 2*s*. 8*d*. luncheon, as he left for an unexpected afternoon's golf. It is a last-minute cancellation of outpatient appointments en masse.

* * *

During the years we lived in a Cockney Terrace in Lambeth it mystified (and sometimes irritated) me, the way all my colleagues up and down would address me firmly as " Mr." The houses, though elegant Georgian of the most sought-after type, had not contained a professional man for a century or so. Consequently Tom the taxi-driver, Ron the docker, Charlie the plumber, and others were a little uncertain about us and it wasn't until our kids were old enough to join in the local destructive activities that the ice (among other things) was broken. Thereafter, baby-sitting was no problem, nor the odd half-loaf on Sunday plus those other little neighbourly services that make urban life possible. In return I catalysed the admission of some ailing relatives to various kinds of hospital and acted as informal P.R.O. for those places when things seemed not to be going right. (How badly hospitals need an effective information service.) So they knew obviously enough that I was a doctor, but still they called me " Mr.".

I never understood why until after I had left the terrace for bourgeois Beckenham. Then on holiday with a cockney couple in a remote farmhouse I was submitted to a further barrage of " Misters ", and I overheard Mrs. Elephant and Castle telling her children severely: " You must not call the doctor 'Dr.', because he is on holiday and not doing his work now." So all that time my old pals had merely been honouring my off duty. How little people understand each other!

* * *

We were surprised and delighted at being invited to a barbecue at the local mental hospital, for my associations with it are tenuous. The feast proved to be a monumental affair, a huge gathering of medical and ancillary staff with their wives or husbands. There was a vast array of food spread out on the immaculate lawn, and an apparently limitless supply of wine. During the evening I heard the M.C. of liquid, the deputy medical superintendent, proudly declaring as he hurried back to the reserve depot, " That makes 80 bottles so far."

One of the staff let me into a secret when I commented on the supreme generosity of the hosts. " As things are here," he said, " one firm deals with the majority of the aged inpatients and naturally that firm gets most of the cremation certificate fees. We decided that the fairest way of dealing with them was to pool them. And this seemed to be a suitable way of disposing of the fund."

A long time later we gave our parting thanks to the medical superintendent, and he replied, " See you next year, all being well?" As we walked away, well satisfied, I felt that the glare of the huge charcoal fire was singularly appropriate.

* * *

News from School.—I have ordered a new sports jacket, but it takes about 3 weeks to come from London. I really am ashamed of my suits now, as they are very small and *rotting* on me. That is not very surprising, is it?

Letters to the Editor

USE OF BRL.1241

SIR,—I read with some dismay in the article by Professor Elek and Dr. Fleming (Sept. 10) that the authors had sprayed large quantities of the new penicillin derivative, BRL.1241 ('Celbenin'), on to an entire hospital ward in an attempt to eliminate nasal reservoirs of staphylococci.

The authors have justified their procedure on the ground that the drug is an "unnatural" compound and that therefore clinically significant resistance to it in the form of an enzyme capable of destroying it is "highly unlikely". Supposed "naturalness" or "unnaturalness" are doubtful criteria for predicting the susceptibility of compounds to attack by microorganisms, as is shown by the wide variety of substances that are readily degraded by common soil bacteria equipped with enzymes that must somehow have previously evolved. It is likewise evident that penicillinase itself is the product of a previous evolutionary process. Further, it is safe to say that at the present time there is knowledge neither of the specific molecular relationships between penicillin, penicillinase, and the genetic apparatus which determines the enzyme's structure, nor of the evolutionary process(es) whereby novel enzymes arise and existing ones are altered. Thus it is difficult to see any justification for the ex-cathedra statement that a mutation resulting in a new or modified penicillinase able to destroy BRL.1241 is "highly unlikely" because the compound is not "natural".

Although in fact staphylococcal penicillinase does not attack the drug and, in the studies published to date, significant resistance has not been encountered in vivo, it is nevertheless true that *Bacillus cereus* penicillinase does hydrolyse BRL.1241 [1] and the finding in this laboratory that *B. cereus* is resistant to its antimicrobial action came as no surprise. Also, resistant mutants of staphylococcus have been isolated readily in vitro in this laboratory and in the laboratory of Dr. Mary Barber,[2] and it is therefore not safe to assume that clinically significant resistance cannot just as well arise in vivo. It is at least certain that if such resistance can be developed, the method used by Elek and Fleming is as well adapted as any other to elicit it. Moreover, the ubiquity of penicillin is well known to have contributed materially to the replacement of penicillin-sensitive staphylococci by resistant ones; should a BRL.1241-resistant strain appear, large quantities of the drug widely distributed can surely be expected to have the same effect.

Admittedly the authors were able to achieve their aim of eradicating nasal staphylococci and in so doing to reduce the incidence of staphylococcal infection on their experimental ward without the development of demonstrable resistance on the part of the organism. Thus the objections raised in this letter may be regarded as theoretical; it is conceivable that the method might be used indefinitely without unfortunate consequences, and it could be argued that the risk involved is acceptable in view of the advantages. This risk must however be assessed in the light of the history of the fight against the staphylococcus which has been a continual effort to find new drugs with which to keep pace with the emergence of resistant pathogenic strains.

We should not lightly disregard this history and its lesson is that the valuable properties of BRL.1241 in treatment of penicillin-resistant staphylococcal infections themselves impose an obligation to cherish and guard it carefully lest history repeat itself once again and we be left with just one more ordinary antimicrobial drug. In accordance with the established principles of antimicrobial therapy, BRL.1241 should be used exclusively for the destruction of penicillin-resistant staphylococci and its primary use should be in the treatment of actual infections. Should it be desired to eliminate such organisms from the nasal passages and elsewhere, then the administrative inconvenience entailed by effecting this on an individual basis is surely not too great a price to pay for the avoidance of the risk inherent in wholesale dispersal of the drug.

Division of Bacterial Physiology,
National Institute for Medical Research,
London, N.W.7. RICHARD NOVICK.

1. Stewart, G. T. *Brit. med. J.* 1960, ii, 690.
2. Barber, M. *ibid.* p. 939.

SMOKING BY ADOLESCENTS

SIR,—Earlier this year you published [1] an appraisal of Edinburgh's vigorous and highly organised campaign against cigarette-smoking. This was carried out in response to the Government's request in 1957 that all local authorities educate the public about the dangers of cigarette-smoking particularly in its relation to lung cancer. The inquiry showed that the campaign had no significant effect in persuading people to give up smoking. The only encouraging result was a change in the public attitude towards smoking in young people. More thought it wrong, and parents with young children over the age of 15 years were now more inclined to regret that their children smoked.

This generation developed the habit in ignorance of the hazards involved because it is less than 10 years since the causal relationship between cigarette-smoking and lung cancer was firmly established. It is surely our responsibility to make sure that our children do not fall into the same trap. This will not be easy because they are constantly exposed to the most subtle and persuasive propaganda. Cigarette-smoking is becoming increasingly common in television programmes where it is particularly dangerous because of the high regard in which the participants are usually held. We know the habit to be already widespread in secondary schools, and in junior schools it is not unknown.

With the present generation firmly in their grip cigarette manufacturers are making every effort to gather our youngsters into their net. Last year they spent £5,000,000 on advertising—more than half of this on television. In 1953, before the days of commercial television, it was £1,000,000. The first quarter of this year showed a startling advance of 60% in advertising expenditure over the first quarter of 1959. It is perhaps not without significance that the post-war bulge babies will be reaching the age of persuasion in 1962–63, and surveys have shown that once a person reaches the age of 18 without becoming an habitual smoker it is unlikely that he will become one. The tobacco manufacturers are concentrating their promotional efforts on teenagers and other young smokers who are not yet set in their ways. In the words of one of their advertisers, they "looked for an idiom in which they could talk to the young people in their own language" and this is very obvious in their more recent advertising approach which shows how life can be more wonderfully enjoyed trailing clouds of tobacco smoke in Elysian surroundings.

1. *Lancet*, 1960, i, 327.

Edinburgh has shown that even the most efficient municipal endeavour is not enough. It is obvious that a high-level national effort is required to deal with a habit to which resistance is so difficult to overcome. Only a few people die from poliomyelitis or diphtheria, yet it is rightly considered necessary to carry out a national immunisation campaign. Many die from accidents on the roads, and through television programmes and other media the importance of road safety is constantly impressed upon us. Lung cancer annually kills four times as many people as are killed on the roads but no equivalent effort is made to fight it. Although the advertising of remedies purporting to cure certain diseases is forbidden by law the Press and television are permitted to advertise tobacco products which can cause avoidable and often fatal disease. It seems reasonable to ask that using the same powerful media action be taken to show the public, and particularly our young people, the other side of the picture.

Dealing with this issue in its recently published report the Joint Tuberculosis Council states that "we are faced with a health problem of great magnitude and not enough has been done centrally to safeguard the public welfare". It goes on to ask, "is it really in the public interest to allow unrestricted advertisement of a substance which reliable evidence suggests is dangerous to health? Are the preventive steps already taken commensurate with the gravity of the situation?" In the opinion of the Council they are not.

We who each year are being called upon to treat an ever-increasing number of cases of lung cancer, coronary thrombosis, and chronic bronchitis must share the opinion of the Joint Tuberculosis Council that this growing threat to the public's health should be approached with a greater urgency than is at present apparent.

Edinburgh. S. LIPETZ.

SIR,—May I support Dr. Learoyd's letter of Oct. 15?

Having worked in hospitals for nearly 30 years, and having been a 20-a-day smoker until June 30, 1954, I agree entirely that it is the adults who stand indicted of mass murder by example. I also agree that action would have been taken about the 20,000 lung-cancer deaths, but for the vested interests—but, Dr. Learoyd, may I as a layman make an appeal to your profession to set a special example.

My many medical colleagues smoke, I believe, more than the average adult male. At a national conference I asked a former Minister of Health if he would advise hospital management committees to discourage smoking in hospitals; he replied that it was not for the central authority to lay down regulations, that it was up to the local committees to decide this problem at their level.

During a recent visit to America, I was impressed by the effort being made in some hospitals to make the hospitals the centre of community health. These hospitals had health museums and encouraged the local people, especially young people, to visit the hospital to learn how to care for their bodies.

If ours is a Health Service, let us stop working a Sickness Service, and let us encourage our young people to live healthily, which among other things means *No Smoking*.

Edinburgh. T. W. HURST.

ARTIFICIAL INSEMINATION

SIR,—This correspondence began as a result of a reference to theological tenets in a leading article. The whole point of my first letter was to point out that the moral theology on A.I.D. cannot, from the nature of things, undergo change or "move with the times". Dr. Jackson, with all due respect, has lifted the argument out of its theological context. My original letter was not concerned with any definitions other than the theological one. It is possible to say with Humpty Dumpty "A word means just what I choose it to mean"; but this cannot alter the definitions given within the confines of moral theology.

Hale, Cheshire. AUDREY F. ROBERTS.

ENZYME DEFICIENCY IN HÆMOLYTIC DISEASE OF THE NEWBORN

SIR,—The very interesting article of Oct. 15 by Captain Weatherall describes red-cell enzyme deficiency in infants in Malaya with hæmolytic disease in the neonatal period. He relates this finding to the type of enzyme deficiency found in certain patients with toxic hæmolytic anæmias due to drugs.[1]

The occurrence of such a hæmolytic condition is of great interest, but I am by no means sure that the findings should be interpreted as indicative of spontaneous intravascular hæmolysis in a group of primaquine-sensitive infants. Evidence that the cells of such individuals will undergo spontaneous hæmolysis in vivo is at present scanty, and in the absence of a history of drug administration or the ingestion of chemical poisons such spontaneous destruction would be surprising.

The principal metabolic abnormality demonstrated in these cases—deficiency of glucose-6-phosphate dehydrogenase (G.-6-P.D.)—has been shown to be present in another disorder, congenital non-spherocytic hæmolytic anæmia.[2 3] In this condition, a severe neonatal jaundice or anæmia is a well-recognised presenting feature,[4] and such children have been previously misdiagnosed as cases of erythroblastosis fœtalis.[5] The other findings reported by Captain Weatherall would be compatible with a diagnosis of congenital non-spherocytic hæmolytic anæmia, and in 1 of the 3 surviving patients a low-grade hæmolytic process was thought to be continuing four years later.

Certain features in the laboratory findings serve to differentiate the congenital non-spherocytic group from those belonging to the primaquine-sensitive variety. Selwyn and Dacie [6] described tests based on observation of the effect of added glucose on fragility and autohæmolysis estimations, while Zinkham and Lenhard [3] have shown that the presence of a reticulocytosis does not, in the congenital non-spherocytic group, result in an increase in G.-6-P.D. activity as is found in the case of primaquine reactors. The red-cell metabolic defect appears to be more severe in the congenital non-spherocytic group, and spontaneous destruction of the cells in vivo is a characteristic finding.

A further large group of cases of neonatal jaundice in children in Malaya was reported by Smith and Vella.[7] They found G.-6-P.D. deficiency in 19 out of 20 cases investigated. This series is not so fully reported as the cases described by Captain Weatherall, and it is not clear whether all were suffering from actual hæmolysis or merely neonatal hyperbilirubinæmia of hepatic origin. It is clear, however, that a syndrome of this type is common in Malaya. If the supposition that these children suffer from congenital non-spherocytic hæmolytic anæmia should be correct, it seems possible that this inheritable disorder is commoner in Malaya than in other parts of the world.

Congenital non-spherocytic hæmolytic anæmia is still regarded as a rare condition, and family studies using the most recent biochemical techniques are infrequent. This

1. Beutler, E., Dern, R. F., Flanagan, C. L., Alving, A. S. *J. Lab. clin. Med.* 1955 **45**, 286.
2. Newton, W. A., Bass, J. C. *Amer. J. Dis. Child.* 1958, **96**, 501.
3. Zinkham, W. H., Lenhard, R. E. *J. Pediat.* 1959, **55**, 319.
4. Dacie, J. V. The Hæmolytic Anæmias. London, 1960.
5. Bruton, O. C., Crosby, W. H., Motulsky, A. G. *Pediatrics*, 1954, **13**, 41.
6. Selwyn, J. G., Dacie, J. V. *Blood*, 1954, **9**, 414.
7. Smith, G. D., Vella, F. *Lancet*, 1960, i, 1133.

combined group of patients in Malaya may represent the largest number of cases available for study so far. The results of further investigations, particularly the application of tests which will distinguish the congenital non-spherocytic group from other hereditary metabolic abnormalities of the red cells, would be of the greatest interest.

Department of Pathology,
Royal Free Hospital,
London, W.C.1. C. S. PITCHER.

ATHEROSCLEROSIS AND CORONARY HEART-DISEASE

SIR,—Surely what distinguishes the pathology of coronary thrombosis in the younger and older age-groups is not the nature but the distribution of the lesions.

Yater et al.[1] showed that in the younger group pathological changes were confined to the heart itself. In the older group, where the condition was part of a generalised atherosclerosis, they were of course more generalised.

This is what makes "young or middle-aged man's" thrombosis a separate and more interesting disease. Presumably, but this has not been written up, many of these cases are not associated with hypertension. This difference may also account for the differential death-rate between men and women under 64. Women (and apparently Seventh Day Adventists [2]) do not get coronary thrombosis as a localised disease.

Possible factors to produce coronary thrombosis in the executive-administrative class have been reviewed recently.[3]

Institute of Directors,
London, S.W.1. H. BERIC WRIGHT.

KIDNEY HOMOTRANSPLANTS

SIR,—In your issue of Sept. 10 I read with interest of yet another successful renal homograft in twins and your leading article on kidney homotransplants in man. While you pay due respect to the advances made in our understanding of homograft acceptance and rejection, work issuing notably from your country, it occurs to me that most papers on tissue transplantation in man fail to consider one important aspect of this problem.

We have learned from the work of Owen, Medawar, Billingham, and others that a lifelong tolerance is conferred upon the heterosexual bovine pairs possessing placental vascular communications which also result in the sterilisation of the female twin—the freemartin. A fact not usually appreciated is that the majority of human single-ovum twins has just such anastomoses in the placenta. In man approximately 80% of "identical twins" have a monochorial placenta. Over 90% of these can be shown to have vascular communications of one kind or another between the two fœtal circulations. Indeed, the flow in these channels occasionally is unidirectional.

Is it not conceivable that transplantation success in human twins could be the result of such anastomoses, as is the case in cattle? In most cases of human tissue transplantation the placental condition is unknown. At this time our knowledge is inadequate to predict whether monovular but dichorial twins would exchange grafts freely. It is not evident from the published reports of successful transplants in twins that it is the genetic constitution of the twins which is the basis for acceptance. It could be an acquired type of tolerance.

The case of Merrill and his colleagues [4] cannot be regarded as necessarily proving dizygous (fraternal) twinning on the basis of unilateral graft rejection, especially not in the light of what they choose to call "consanguinity" in 25 blood-groups. Other authors use such concordance as main arguments in favour of identity. In fact, it is difficult and often impossible to establish proof for monovular origin in dichorial twins. Merrill et al.[1] were cautious to label the twins as non-identical rather than fraternal. It is well known that non-identical monovular twins occur frequently. Since their dissimilarity can extend to severe unilateral malformations one can reason that it could also, on occasion, involve histocompatibility genes.

The point I wish to make is that obstetricians should begin to document carefully the placental conditions in twins for the benefit of the twins and science.

Department of Pathology,
Dartmouth Medical School,
Hanover, New Hampshire. KURT BENIRSCHKE.

TREATMENT OF URTICARIA

SIR,—Having heard something of Dr. Sidi's results (Oct. 15) in the treatment of urticaria with antimalarials, and prompted by the experience of Sir Charles Dodds (Oct. 22), I have recently carried out a clinical trial of proguanil ('Paludrine') in the treatment of chronic urticaria. This was carried out at St. John's Hospital for Diseases of the Skin, where my colleagues kindly sent cases to me for study.

18 patients have taken part in the trial, of whom 9 were men and 9 women. Ages ranged from 20 to 72 years. Duration of urticaria ranged from four weeks to three years.

Of these patients 9 were given one period of treatment and after an interval later re-entered the trial, so that altogether 27 observations have been made.

Capsules were prepared containing 100 mg. of proguanil or 100 mg. of sodium bicarbonate. Each patient was given 28 capsules of one or other kind with instructions to take one capsule twice daily for a fortnight. Proguanil or sodium bicarbonate was serially allotted to patients according to a previously prepared random order. When patients re-entered the trial a second time they were treated as new patients, and therefore received either the same or a different treatment from the one they had had the first time. Neither the patient nor the doctor knew which treatment was being given until the conclusion of the entire series.

The results were as follows:

	Cleared	*Improved*	*Total Improved*	*Doubtful*	*Failed*
Proguanil ..	3	2	5	3	5
Bicarbonate ..	0	2	2	1	9

Cleared means that all urticaria had ceased by the time the patient was seen at the end of a fortnight's treatment.

Improved means that the patient stated that the urticaria was less than before treatment and less than had previously been experienced as a spontaneous fluctuation.

Doubtful means that improvement observed, if any, was within the range of previous spontaneous fluctuation.

Failed means that during the fortnight's treatment the eruption remained unchanged or became worse.

2 patients failed to re-attend for treatment, leaving 25 who were available for assessment.

Of the 3 patients who cleared with proguanil, 1 had previously shown improvement on bicarbonate. Of the 2 patients who improved on proguanil, 1 later re-entered the trial and failed on proguanil; the other later re-entered the trial and made a similar improvement on bicarbonate.

The assessment of the value of treatment in chronic urticaria is difficult for three reasons: first, because the disorder itself fluctuates in severity in an unpredictable way and eventually clears up or remits independently of treatment; second, because at the time of examination the eruption is often not present and the estimation of its severity has to be made entirely by the patient; third, because chronic urticaria is much subject to psychological influences and the results of treatment are likely to be

1. Yater, W. M., Traum, A. H., Brown, W. G., Fitzgerald, R. P., Geisler, M. A., Wilcox, B. B. *Amer. Heart J.* 1948, **36**, 334.
2. Wynder, E. L., Lemon, F. R., Bross, I. J. *Cancer*, 1959, **12**, 1016.
3. Wright, H. B. *Practitioner*, 1960, **184**, 765.
4. Merrill, J. P., Murray, J. E., Harrison, J. H., Friedman, E. A., Dealy, J. B., Dammin, G. *New Engl. J. Med.* 1960, **262**, 1251.

considerably influenced by suggestion. Because of this I believe that only a blind controlled trial is likely to give reliable information.

The trial which I have briefly mentioned had negative results, but one cannot of course prove that proguanil was ineffective. One can only say that in these 25 tests no convincing evidence of effectiveness emerged. I appreciate, of course, that proguanil is not the same as amodiaquine, which Dr. Sidi and Dr. Reinberg used; it was chosen in my series because of its freedom from side-effects.

These results do not necessarily indicate that the antimalarials are never effective in chronic urticaria. One may well suppose that the symptom is the end-result of a variety of different causes or mechanisms and that an antimalarial may break a link in pathogenesis in one case and not in another. This may explain the occasional remarkable case where the effectiveness of an antimalarial seems to be undeniable although it cannot be regularly obtained in other patients.

London, W.1. F. RAY BETTLEY.

COMMUNITY MENTAL CARE?

SIR,—Psychiatry is following good precedents as it evolves and develops a social conscience. It is turning from a preoccupation with those human abstractions of natural processes that are labelled " diseases " to prevention and to the promotion of mental health.

Mental health is, however, too vast and too important to be delegated to any one section of medicine. Fortunately, the barriers that isolated psychiatry from the main currents of medicine (a subject discussed in your leader of Oct. 15) are being eroded from both sides. Your report that general practitioners and medical officers of health recently conferred with psychiatrists on mental health is a welcome illustration. Others among us are also concerned, and pædiatricians especially so, if only because so many mental disorders have their roots in the early years of life.

But mental health is too vast and too important to be delegated exclusively even to the medical profession. Allies are needed outside medicine and its traditional associates (such as psychologists and social workers). Geneticists, biochemists, sociologists, and anthropologists surely have fundamental contributions to make. So also have those non-medical agencies concerned with moral welfare, with family life and with education—of parents and of children. An enterprising pilot scheme inaugurated by Dr. S. Lebovici in a whole sector of Paris has already shown that school teachers, for example, can play a very important part in the prevention and early case-finding of mental disorders.

" Is the community ready for prevention?" was asked at a recent conference on preventive psychiatry.[1] While that question is being pondered some of its implications will also be weighed. To prevent assumes that we know what is undesirable. To some extent we do know, but we need to know much more. In *The Common Sense of Science*, J. Bronowski quotes William Clifford, geometer and philospher, who wrote of scientific thought: " The truth at which it arrives is not that which we can ideally contemplate without error, but that which we may act on without fear ". I believe that in the field of mental health, psychiatry and medicine should augment their forces in order to establish a substantial basis on which to act without fear.

Bristol Royal Hospital for Sick Children, Bristol. JOHN APLEY.

1. *Times Educational Supplement*, Sept. 30, p. 387,

CONSERVATION OF THE OVARIES

SIR,—Your annotation of Oct. 22 on conservation of the ovaries at hysterectomy is timely. The removal of *normal* ovaries before the menopause as prophylaxis against subsequent carcinoma is physiologically and psychologically indefensible. Even if the ovaries are cystic an attempt should be made to conserve ovarian tissue. In the rare event of the pathological examination revealing malignancy then I admit a further laparotomy would be necessary. But I believe this course is preferable to the wholesale sacrifice of ovaries, normal and cystic, that is such a common practice.

If we accept Jeffcoate's [1] estimate that only 1 case of ovarian cancer can be prevented at the expense of 5000 hysterectomies and Schabort's [2] recent figure of 2 in 5000, then there is no place for routine oophorectomy. Osteoporosis and atherosclerosis are now recognised as complications of the normal and artificial menopause but the profound psychological disturbances that follow the latter have received insufficient emphasis. It is the family doctor who has to deal with these and not the surgeon since the patient never wants to see him (or her) again.

A woman has an emotional attachment to her uterus and ovaries and it is unfortunate that her gonads, unlike the testicles, are not in an extracorporeal pouch secure from unnecessary extirpation.

University College Obstetric Hospital, London, W.C.1. W. C. W. NIXON.

THE RESERVED £1 MILLION

SIR,—As members of the General Practice Reform Association, we note with approval the aim of the joint working party to raise standards of general practice, and to investigate methods of distribution of remuneration which will help to achieve this end.

We believe that the most effective way of improving the quality of practice is to give every possible encouragement to the practitioner to keep up to date and to extend his knowledge of medicine, and to cooperate more closely with his colleagues in the hospital service.

Accordingly, we should like to suggest that the £1 million be used to finance the setting up of paid clinical assistantships for N.H.S. general practitioners in general hospitals. We suggest that such clinical assistantships should be made available, in rotation, to all general practitioners who desire them, and in as many clinical specialties as possible. Clinical contact between consultant and general practitioners would prove stimulating to both parties, and the hospitals would benefit in the long run through having fewer patients referred for consultant opinion.

At present, general practitioners who work part-time in hospitals are remunerated from hospital sources. We can see no insuperable practical objections, however, to altering this system so as to pay for clinical assistantships out of the central pool, and we feel that the benefits of our proposal would outweigh any minor administrative difficulties. At the rate of remuneration recommended by the Royal Commission for general practitioners working in hospitals (£215 p.a. per notional half-day) the £1 million would enable every principal in the N.H.S. to serve as clinical assistant, in one or more specialties, for one half-day per week for six months in every thirty months. All G.P.s would be enabled to share in the money, and controversial proposals for " merit awards " for particular

1. Jeffcoate, T. N. A. Principles of Gynæcology; p. 667, London, 1957.
2. Schabort, J. W. *Trans. Coll. Phycns Surg. Gynæc. S. Afr.* 1960, **4**, 11.

practitioners, or for payment for specified items of service (involving more paper work in making claims) would be obviated.

A. C. McLEISH
Chairman
A. C. J. SAUDEK
Secretary.

General Practice Reform Association,
London, N.W.6.

TRUE HERMAPHRODITISM AND KLINEFELTER'S SYNDROME

SIR,—Perhaps if we had entitled our report of Oct. 1 "Chromosome count in a hermaphrodite who *presented* with some of the features of Kleinefelter's syndrome" we would have described better what occurred and would have avoided some of the criticism of Dr. Bishop and Professor Polani (Oct. 23). We still maintain, however, that when a male person presents with eunuchoid proportions, female pubic hair, absent facial hair, gynæcomastia, and a small testis (how small must it be!) then the possibility of Kleinefelter's syndrome must be considered in view of its reported relative frequency. If he turns out to be "chromatin-positive" then we feel that all these facts constitute "some features" of the syndrome whatever the eventual diagnosis may turn out to be. We believe also that the pathology of the testis was quite comtible with the diagnosis, especially since there was no evidence at the time of overstimulation of the testis by the pituitary.

There is no doubt now that we should initially have been more alert to the possibility of hermaphroditism, and it was in an effort to warn others who might be placed in a similar position to ourselves that we included any reference to Klinefelter's syndrome at all. By changing the time factor only slightly we could easily have reported the chromosome analysis in a hermaphrodite whom, in retrospect, we had diagnosed clinically with the same assurance as Dr. Bishop and Professor Polani.

R. R. GORDON
F. J. P. O'GORMAN
C. J. DEWHURST
C. E. BLANK.

City General Hospital,
Sheffield.

PERPHENAZINE IN HUNTINGTON'S CHOREA

SIR,—Dr. Pakenham-Walsh (Oct. 1) is to be congratulated on what may be an important therapeutic observation. No doubt in his desire to be brief one or two points remain obscure and on these we would welcome enlightenment:

(1) The grounds on which he makes the diagnosis of the "hereditary chorea" of Huntington.

(2) Why he does not include in his therapeutic target the numerous choreo-athetoses accompanied by progressive intellectual deterioration arising from other causes.

(3) Why he does not include cases of choreo-athetosis not associated with dementia.

STELLA CONWAY
R. H. BOARDMAN.

Herrison Hospital,
Dorchester.

*** We showed this letter to Dr. Pakenham-Walsh whose reply follows.—ED.L.

SIR,—The diagnosis was made essentially on clinical grounds. Both patients exhibited characteristic mental and physical symptoms and signs. I agree that in case 1, as far as we were able to determine, we could obtain no unequivocal evidence of a positive family history, and in case 2, this could not be obtained because he was a Ukrainian displaced person and no history whatsoever was available from his family background. In spite of these omissions, however, the cases were so typical that there was little hesitation in diagnosing them as Huntington's chorea.

As far as other choreo-athetotic conditions are concerned, we will certainly attempt a diagnostic evaluation and treatment in the light of our present therapy. This therapy appeared to me to be so significant, however, and it seemed of some interest and importance in such an intractable state, that publication was justified if only to draw attention to the potentialities of the drug and if possible to confirm this with other centres.

R. PAKENHAM-WALSH.

Lancaster Moor Hospital,
Lancaster.

SPORTS MEDICINE

SIR,—I do not agree with Dr. Troup's statement, in his interesting article of Sept. 24, that "medicine is not very clever when it comes to coping with the sprains and strains to which athletes are subject". It would be more true to say that the knowledge of how to treat these disabilities has been known and practised with good results, for many years, by a very small minority of the profession. Several excellent writings on the subject have been made in the past by many authors—e.g., Sir Robert Jones, Sir Morton Smart, Bristow, Mennell, Tucker, and latterly Cyriax, as mentioned in Dr. Barbour's letter of Oct. 8; but little interest has been shown by the profession in learning from their works.

Until three years ago I was in the R.A.M.C., where I had considerable experience in the treatment of athletic injuries, treating them along orthodox lines, and I thought that I knew a great deal about their management. Now, however, I realise that the methods I used did not produce the quick results which can be obtained by following a few simple rules. Athletic injuries are a specialised field, and yet good results can be obtained by anyone sufficiently interested to learn these few basic rules, most of which are frequently broken even by prominent orthopædic surgeons.

These rules are:

(1) An exact diagnosis must be made. If complete rupture of a ligament or tendon is diagnosed, then immediate operative repair must be performed.

(2) Prompt reduction and elimination of traumatic swelling. This is accomplished by aspiration of hæmatomas, or incision and evacuation of clotted hæmatomas; injections of hyaluronidase to assist the spread and absorption of traumatic swelling and effusion; the use of pressure bandages; physical treatment consisting of massage with the limb in elevation and faradism to the affected muscles.

(3) Rest and support the damaged structures by means of an easily removable splint, so that home treatment consisting of remedial exercises in relation to contrast baths and self-massage can be performed up to four times a day, and also so that physical therapy can be given.

(4) Remedial exercises are given. Isometric exercises which are performed with the splint on, to maintain the power of the muscles, and isotonic exercises with the splint removed to coax and increase the range of movement of the joints affected and prevent the formation of adhesions. These must be very carefully supervised, a correct balance between rest and activity being obtained: the dictum is "rest from strain, but exercise without strain".

(5) Correcting postural faults and teaching the patient "active alerted posture".[1] This ensures that each joint at all times is under muscular control so that strain is removed from the affected joint, the injured structures thus recovering more quickly. This also assists materially in preventing recurrences.

(6) During the recovery period it is essential to make sure that muscles which have been damaged, or muscles acting on a

1. Tucker, W. E. (1960) Active Alerted Posture. London.

joint which has been injured, regain their full length in relaxation as well as their full power of contraction. Otherwise when violent activity is resumed muscle tears or symptoms of joint strain will recur. This full relaxation is obtained by massage, by gentle stretching of the muscles, and by manipulations of the joints during the healing process to prevent contractions. Attention must be paid to the range of movement of the joints above and below the affected joint to ensure this.

(7) Occasionally in spite of this treatment full functional recovery is obtained only by manipulation of a joint or stretching of a muscle under general anæsthesia.

London, W.1. R. P. GOULDEN.

ADMINISTRATION IN MENTAL HOSPITALS

SIR,—At this hospital I think we have found the answer to the problem of administration in mental hospitals, although, of course, this solution, like any other, has its defects.

We have divided the hospital into three independent clinical teams of 300 beds each. Each team has its own admission wards and long-stay wards and each team has its own outpatient clinic. The teams consist of a consultant in charge, S.H.M.O., and two junior doctors, one being a registrar and the other a J.H.M.O. The third team has two consultants who share responsibility on an equal basis, each consultant having his own share of the admission beds. The consultants have absolute clinical control of their teams. It is firmly accepted that the consultant is fully responsible for the patients under his care and that the medical superintendent has no right to interfere in his clinical freedom. Each consultant, therefore, is responsible for his own correspondence, which does not go through the medical superintendent's office.

Each consultant and S.H.M.O. are " on take " for a week at a time, and unless a general practitioner asks for a particular consultant the one " on take " is responsible for all domiciliary visits and emergency visits to other hospitals in the area. All acute admissions go on to the ward of the firm " on take " for the week.

The medical superintendent has his own firm, which he shares on an equal basis with the consultant who is also in charge of the E.E.G. department.

Each firm has its own social worker, assistant matrons, chief male nurse, and mental welfare officers. At the present time the distribution and administration of the nurses is still essentially controlled from the nursing office of the respective sides of the hospital, but we rather hope that eventually each firm will be responsible entirely for its own nursing organisation.

The medical superintendent is the coordinator of the teams in the sense that he is chairman of the weekly senior staff conference. He is the liaison officer between medical staff and management committee. He attempts to act as a mediator and moderator between medical and nursing staff on the one hand and administrators on the other (areas of traditional misunderstanding and friction). As far as the hospital management committee is concerned he is answerable to them for the efficiency of the medical work of the hospital. Although there is something to be said for doing away altogether with a " board-appointed " superintendent and adopting the general-hospital pattern of medical staff committees, the following points should be borne in mind:

(1) However good the lay administrator may be, in the last analysis it must be the medical staff who should approve or disapprove of such things as plans for new wards, their furnishing, and various other domestic matters which do in fact have a great effect on the patients' lives, especially in a mental hospital. This work of liaison can perhaps better be done by a man who is permanently appointed to the office, because he has powers of decision and authority not available to an elected chairman of a medical staff committee. Therefore, if the medical side are to have this effective say, it can be better done through one doctor who, being permanent, the administration get used to, who has the right to attend all H.M.C. meetings, and who is officially recognised as responsible for medical organisation, because then the H.M.C. have to take more notice of his monthly reports than the resolutions of medical advisory committees. In addition he is able to take decisions on the spot rather than having to refer matters back to committees which may only meet once a month.

(2) Mental hospitals are only dealing with one type of patient, and therefore it is much easier for one doctor to act as director than in a general hospital in which there are many different types of patient. During the next ten years we shall probably see mental hospitals with and without superintendents, and it will be possible then to judge the merits of the two systems. One thing, however, is certain: that the old autocratic administrative superintendent is a person of the past. The modern superintendent, director, or coordinator must be first a clinician with his own team; and his administrative duties are those of coordinator, catalyst for new ideas, moderator and authoritative voice of the medical staff, although like any chairman he is free to express his own independent opinions apart from those of his colleagues but not instead of them as used to happen in the past.

Towers Hospital, Humberstone, Leicester. H. B. KIDD.

PERITONEAL SPLASH: A PHYSICAL SIGN

SIR,—The letters by Mr. Lane Roberts (Sept. 24) and Mr. Smiddy (Oct. 15) on the signs of perforated ulcer are very interesting. Like Mr. Smiddy, I have found that this sign can be somewhat unreliable, and that even under anæsthesia both false positives and false negatives are obtainable.

May I draw attention to another physical sign in perforated ulcer which seems to receive little attention? If a patient who is suspected of a perforated ulcer is raised actively or passively into a sitting position, he often complains that the pain is produced high in the interscapular region. This is often present when many other signs are absent, and is useful in the longstanding perforation, where the only appearances are of general peritonitis, but where a history of sudden onset of pain raises the possibility of a perforated peptic ulcer. It is not present in my experience with perforations of other viscera.

The General Hospital, Birmingham. GEORGE T. WATTS.

SCHOOL DENTAL SERVICE

SIR,—The future of the school dental service, which was dealt with in your annotation of Oct. 15, was also discussed in last week's *Local Government Chronicle*. Both journals suggested that the school dental service should be completely reshaped. This seems to be a drastic step to take when a few adjustments in the present administration should solve most of the problems which exist at present. There seems to be no need to set up a separate department, as the administrative services at present available in the health department can cope with the work of the school dental service. Provided the principal dental officer is given proper status he will be no more controlled by the medical officer of health than is the ophthalmologist who works for the health department on a sessional basis.

The only changes that appear to be necessary are firstly that the salary scale of a dental officer should be an approximate assimilation of the assistant medical officer and senior medical officer scale. That is £1300–£2200. Where there is an establishment of four or more dental officers there should be a principal dental officer, who should be paid the same salary as a principal medical officer. An officer entering the service should receive one increment for every year he has spent in military or civilian practice.

These changes in the salary scale, along with inducements such as a car allowance, five-day week, and paid evening sessions, which the more enlightened authorities already provide, would make the service more attractive

and would probably encourage some of the dentists in the older age-group to transfer to the service when they felt they could no longer keep up the pace required in private practice.

MEDICAL ADMINISTRATOR.

ASSESSMENT OF HEPATIC SIZE, SHAPE, AND CONTENT

SIR,—Your annotation of Oct. 1 does not mention a valuable method for determining the liver size. By peritonoscopy a suspected hepatomegaly can easily be confirmed and the relations of a palpable abdominal mass to the liver and gallbladder verified. (Without laparotomy the diagnosis of a Riedel's lobe and a polycystic liver can be made only by peritonoscopy.) The method is of great value for identifying hepatic metastases before operation, and only tumours deep in the hepatic parenchyma cannot be seen. Explorative laparotomy, as suggested by Mr. Grimshaw (Oct. 8), may thus be replaced in most cases by peritonoscopy, which, when not combined with biopsies, &c., is almost completely safe and is well tolerated by the patients.

Rigshospitalet, Copenhagen. K. WINKLER.

THE BORDERLINE FOR SEVERE SUBNORMALITY

SIR,—With the start of the Mental Health Act (1959) on Nov. 1, the problem of the borderline between conditions of incomplete mental development becomes an important practical consideration.

In mental-deficiency practice in the past, it has been customary to differentiate degrees of incomplete development of mind in terms of, on the one hand, the "low-grade" (idiots and imbeciles), and on the other, the "high-grade" (feeble-minded), with an I.Q. of about 50 commonly acknowledged as the dividing-line. Below this level, pathological ætiology predominates and the prognosis for an independent life is exceedingly poor, and above it, subcultural ætiology and a relatively good prognosis are common. This, too, accords well with the observation that above I.Q. 50 or 55 intelligence seems to be distributed in a Gaussian fashion; hence the "high-grade" defective is essentially a "low-grade" normal, whereas the low-grade defective personifies abnormality.

The Royal Commission on the Law relating to Mental Illness and Mental Deficiency (1954–57) suggested application of the term "severe subnormality" to those whose "general personality is so severely sub-normal that the patient is incapable of living an independent life. This group includes all patients at present classified as idiots and imbeciles and *some* (our italics) of those now classified as feebleminded." (Report of the Royal Commission, para 17). Later, in the same report (para 193), an intelligence quotient below 50–60 is quoted as "a pointer strongly indicative of a personality so seriously subnormal as to make the patient incapable of living an independent life." Life is of course rarely, if ever, absolutely independent in modern society. Nevertheless, some amenable but at the same time relatively incompetent patients can be trained to earn their living and become tolerably independent in the community, despite their I.Q.s being in the 50–60 range, whereas others, less amenable to advice and help, fail to do so despite having I.Q.s in the 60–90 range.

In the Mental Health Act itself, which of course arose from the Royal Commission's report, severe subnormality is defined as "a state of arrested or incomplete development of mind which includes subnormality of intelligence and is of such a nature or degree that the patient is incapable of living an independent life or of guarding himself against serious exploitation or will be so incapable when of an age to do so." "Nature or degree" are the operative words, and their interpretation is the problem.

In January, 1960, the Ministry of Health (Estab. 3039/25) commented on the new terminology and stated that "severe subnormality" will apply to "a large proportion of patients now classified as idiots or imbeciles *and perhaps rather more than half of the feebleminded*" (our italics). Later still, a Ministry memorandum on parts I, IV-VII, and IX of the Mental Health Act refers to the subnormal as "intellectually dull but their main trouble is often emotional instability". Assuming, as we must, that the term "intellectually dull" is used deliberately and, in conformity with general usage, relates to I.Q.s between 70 and 85, it may be inferred that most patients with I.Q.s below 70 are now expected to be included in the severely subnormal class. Thus the dividing line set somewhere in the 50–60 range by the Royal Commission seems to be moving to 70 or perhaps even to 75, and most patients under care with I.Q.s below 70 stand in peril of being classed as severely subnormal, with the attendant implication (manifestly untrue for many of them) that they may be incapable of leading an independent life when of age to do so. This hospital, for example, has for many years trained such persons for industrial work and normal jobs at normal wages, so that after two years or so in the community they have been discharged from care to an independent life. Official guidance thus appears to be at variance with the spirit of the Royal Commission's report, the Mental Health Act itself and the experience of hospitals with progressive policies of training or treatment, not to mention the recommendations of the World Health Organisation. Moreover, the extended category of the severely subnormal would contain patients with conditions of greatly diverse ætiology, with present assets as disparate as those of the "man-in-the-street" and Albert Einstein, and with vastly different prognoses.

In principle, therefore, it would seem to be more in accordance with the intentions of the Royal Commission that the definition of severe subnormality (which has much in common with that of imbecility in the 1927 amending Act) should continue to apply to those in the now obsolete categories of idiot and imbecile, and those "higher-grade" patients with I.Q.s between 50 and 55 or even up to 60 whose prognosis seems poor because of personality defect. Many witnesses heard by the Royal Commission drew attention to the harm done by mixing patients of differing grades, but at least it was recognised legally at that time that there *were* different grades of patient within the 0–70 I.Q. range. If severe subnormality is to be given a widely extended interpretation, the recognition of differences in both present status and prognosis will tend to disappear, and many of the dangers, of which the Royal Commission, and interested members of the general public were well aware, will tend to recur. Blanket categories are apt to lead to stereotypes and then to blanket forms of treatment—or lack of it.

It must be admitted that our suggestions, which were in fact originally advanced by the Royal Commission, would lead to administrative difficulties in application of the Mental Health Act where older patients under care are concerned. Owing to lack of adequate training facilities in the past, to national unemployment, and to the effects of long-term residence in institutions, many of these though only of subnormal intelligence are too incompetent socially to take an independent place in society. But these are essentially administrative problems, and it would be disastrous to sacrifice hard-won principle to short-term advantage.

The Manor Hospital, Epsom, Surrey. J. F. MACMAHON
A. D. B. CLARKE.

MODERN CLINICAL BIOCHEMISTRY

SIR,—There are many occasions when inspired comments about clinical biochemistry are best ignored. Thus it came about that the nonsense written in the Widdicombe File [1] was allowed to pass without comment. But Professor Cappell cannot be allowed to get off scot-free with his article of Oct. 15 entitled Pathologists at the Crossroads. Since it is on only rare occasions that the subject of clinical biochemistry (as a subject) receives any attention in the medical press of this country, perhaps you would allow a professional biochemist to reply at some length to Professor Cappell and to the many others like him.

Professor Cappell regards biochemistry (syn. chemical pathology) as one of the "four branches of pathology". This is not so, for in the hospital where we both work my department of biochemistry is most certainly not a branch of his department of pathology, nor is the biochemistry which I practise a branch of the pathology which he practises. Biochemistry is a science and is defined as the application of chemistry (repeat, *chemistry*) to biology—in the case in question, to that branch of biology which deals with human disease. All biochemistry, without exception, is applied chemistry, and however unpalatable this may be to those who are not scientists, there is nothing that can be done about it. Biochemistry is not, and never was, a branch of pathology.

Much of the routine work in a modern hospital biochemistry department is necessarily carried out by technicians (exactly as in pathology departments), but these biochemical technicians are highly skilled analysts working alongside qualified scientists to whom they can turn for professional advice and assistance. It is deeply regrettable that Professor Cappell should describe these highly qualified scientists as "other workers not medically qualified". It is this deplorable attitude, in very words such as these, which makes it all but impossible to recruit young science graduates into hospital biochemistry departments.

Automation cannot be dismissed in the few words employed by Professor Cappell. There are many snags to it. All clinicians are familiar with the difficult case of acute metabolic upset where 6 to 8 separate chemical analyses must be carried out in the minimum of time in order to help save life. This is the most important part of hospital biochemistry, and in such cases automation is worse than useless. The modern biochemist uses every effort to wean the clinician away from "large numbers of simple repetitive tests" (few of which are as "simple" as they seem), and the bad old days of doing blood-ureas up one side of the ward and blood-sugars down the other, have almost entirely disappeared. In place of this, the clinician has an ever-increasing choice of better and more specific methods of investigating metabolic disturbance. Yet, we must confess that the blood-sugar/blood-urea mentality still persists in certain quarters.

Professor Cappell states that much of the routine biochemistry can be carried out by "workers who are capable of following given instructions". There is no surer way of landing in trouble. It is the most fundamental of all axioms in science that the worker (whether a junior technician or a qualified graduate) must *understand* what he is about to do, before he begins to do it. Not even the most experienced scientist dare ignore this axiom.

The idea that the medical graduate can aspire to a reasonable knowledge of biochemistry by "a year of fundamental study in chemistry" is laughable. Does he start with the Law of Constant Proportions and finish up with heterocyclics—perhaps with a basinful of thermodynamics thrown in somewhere? The major curse of modern clinical biochemistry is that so many people think it a simple little subject that can be mastered in a few months' study. The vision of the young pathologist with "a certain foundation in each of our four disciplines" clearly demonstrates how far the writer is out of touch with modern science. No doubt he would be delighted to have all these four separate subjects grouped together as "pathology" for the greater glory of his own subject. But in the case of biochemistry, which demands so much specialised knowledge of pure chemistry, a "certain foundation" is just not good enough in these days. The hospital of today demands, and is entitled to get, something a good deal better than one-quarter of a jack-of-all-trades who can turn his hand to any odd job. In this modern scientific world, the part-time amateur is definitely out. Pathologists cannot put the clock back half a century.

Admittedly, it is a tragedy that there are large areas where "Clinical Pathology" still flourishes—even in 1960 A.D. There is not much that we biochemists can do about it; we are seldom consulted; the powers that be invariably go to the pathologist for advice. These areas, where some of the biochemical services are primitive beyond belief, will continue to exist just as long as the clinicians are prepared to tolerate them.

One must have some sympathy for the plight of the poor young pathologist described by Professor Cappell, but if you stand at the crossroads for five or more years, trying to look north, south, east, and west simultaneously, what else do you expect but a pain in the neck? This wretched creature will probably finish up with a diploma in clinical pathology (which Professor Cappell curiously omitted to mention in his article), land in a tenth-rate laboratory, and spend most of his life doing routine blood-ureas—and serve him right for being such a fool! There is only one end to all this. Let the pathologist stick to his microscope and leave biochemistry to those who are qualified to practise the subject.

The Western Infirmary, Glasgow.

E. B. HENDRY.
Consultant Biochemist.

1. *Lancet*, 1960, i, 1242.

ESSENTIAL HYPERTENSION

SIR,—You published on Oct. 8 and 15 two papers whose authors appear to make quite different assumptions about the nature of essential hypertension. Professor Brod tests a hypothesis about hæmodynamics in hypertension that is derived both in concept and in method from psychosomatic research. The concept of hypertension as a stress disorder was extensively discussed at a conference at the Royal College of Physicians in May, 1958, and I would recommend a study of the proceedings [1] to those who want to understand the background to Professor Brod's thinking about research.

The relevant observation is that hypertensive episodes spontaneously arising in people without cardiovascular disease, or that are experimentally provoked by an investigator, have a consistent emotional basis. This is an emotion best described as one of aggressive resentment arising in frustrating social and domestic situations and having an impulsive tendency to handle the situation by an inappropriate muscular aggression that has to be held in check.

These observations from the psychiatrist's couch lead to a prediction that an increased flow of blood in voluntary muscles should be a feature of hypertension that will become marked during pressor responses. Brod has shown just this. It also explains why he can make apparently sweeping conclusions, thus (p. 778): "the rise of blood-pressure . . . at any rate in the early stages, can accordingly be explained by the hypertensive being in a state of more or less permanent readiness for muscular action. This explanation differs from previous ones in that essential hypertension is not regarded as something newly acquired but simply as the result of disturbed regulation

1. The Nature of Stress Disorder. Society of Psychosomatic Research. London, 1959.

of one of the fundamental hæmodynamic responses of the organism."

To turn to the paper from the Social Medicine Research Unit, I know that the supporters of bimodal distribution *and* the supporters of continuous distribution of diastolic pressure in the population are all aware of some of the evidence about stress, but there is no evidence that they are integrating this into their thinking about this problem. I think the stress concept allows that a continuous distribution in young adults may become a bimodal one in the middle-aged, when a psycho-physiological response has become exaggerated into a disease of blood-vessels. Professor Morris aims his research at the "common high blood-pressure without evident cause in middle age", but I am sure from my own work and from that of Hines, whose writings are too well known to need quoting, that if we want to understand the nature of hypertension we must look at its uncomplicated beginnings in young adult life, where it seems to appear silently as a transient stress response from a quasi-normal baseline. Begin here if you want to know the natural history of hypertension.

For my part I do not think the primary disorder is high blood-pressure, but an excessive excitability of the diastolic pressure, that is one aspect of an excitability of the whole person. This is why casual readings are so suspect. There must be several genetic elements, but stress findings indict cultural elements which should be allowed for in evaluating resemblance in close relatives whom you may expect to have more family stress in common than they have inheritance.

May I end on a thought-provoking question that was put from the chair at the conference on stress disorder in 1958 by Dr. Fraser Roberts: "Why should it be that so many of the diseases which are regarded as psychosomatic are the diseases which have a genetic component?" This question is a pointer towards a more rewarding multicausal approach. Perhaps, like Professor Brod, investigators will have to start thinking about the whole person in his human setting.

Cranbrook. JOHN HAMBLING.

SURGICAL REMOVAL OF BRANCHIAL SINUS

SIR,—I was interested to read Mr. Small's account (Oct. 22) of this operation. I have not enough experience to comment on the debatable point of whether the lesion is primarily a fistula or a sinus, but I do recall one case where the dissection was facilitated by the preliminary injection of the track with gentian violet.

In this instance the track seemed to end short of the pharyngeal wall, but I was intrigued to hear from the anæsthetist after the operation that the pharynx contained a lot of blue dye. Fortunately a cuffed and inflated endotracheal tube had been employed and no harm resulted.

Mr. Small states that with the method he describes, intubation is preferable but not essential. I feel, however, that regardless of technique—and despite the hazard recently reported by Dr. Pryer and his colleagues (Oct. 1)—where the incidence of a fistula as opposed to a sinus may be as high as a third of the cases, a cuffed and inflated tube should always be used.

Stobhill General Hospital. F. T. CROSSLING.

NAMES OF DRUGS

SIR,—Would it not be possible for your journal to help further in the clarification of the vexed and complicated subject of the names of drugs?

In *The Lancet* of Oct. 15, in a leading article on "Tranquillisers in Psychiatry", you discuss, amongst other drugs, the use of methaminodiazepoxide. The trade name is not mentioned. In the correspondence columns are five letters concerning the side-effects of 'Librium'. Neither the heading of the correspondence column nor any of the letters mentions the pharmacopœial name. Only references to previous correspondence connect the two names. The trade names of some of the other drugs mentioned in the leading article may be less easy to find.

The equivalence of pharmacopœial and trade names of drugs more recently introduced cannot yet have reached the standard works of reference, and it would be helpful if equivalent names were cited more frequently in current literature.

Bedford. R. G. MILLER.

*** We are sorry we were not more helpful on the occasion Dr. Miller mentions. In editorials we normally give approved or chemical names in preference to proprietary names, of which there may be several. There is as yet no official approved name for methaminodiazepoxide ('Librium') and we used the non-proprietary name now in use. Unfortunately we failed to include it in the group of letters published on Oct. 15.—ED. L.

DIAGNOSIS OF FAT-EMBOLISM

SIR,—After reading Dr. Sevitt's useful paper of Oct. 15, I am prompted to draw attention to the valuable help in the diagnosis of fat-embolism afforded by ophthalmoscopy, particularly in cases with "cerebral" symptoms. The embolus can be seen as a highly refractile globule, lodging usually at the fourth or fifth branching of a retinal artery, the branches beyond being invisible. This has repeatedly proved of invaluable help when peculiar neurological syndromes have presented in circumstances suggesting the possibility of fat-embolism. The clinical picture may at times indicate dysfunctions in the mid-brain or pons, and for that reason the term "cerebral" is inaccurate. Obviously the disturbances produced must depend on the chance distribution of the major showers of emboli, and for that reason the pattern of neurological disturbance in these cases is far from stereotyped.

When the emboli have lodged in the retinal arteries for a day or more their presence can be deduced by the finding of several small white patches with fluffy margins peripherally in the retina.

Retinal emboli can be seen in cases with negative sputum and urine, and before petechiæ appear.

Frenchay Hospital, Bristol. G. L. ALEXANDER.

SIR,—I was extremely interested in Dr. Sevitt's article. He states that "aids to diagnosis would be most helpful in the severe cases without a rash". Although I can make no claim to experience, having seen, in my capacity as ophthalmologist, only one case, might I make a plea for routine examination of the fundus oculi in such cases?

A child of 9 was knocked down by a car and sustained a comminuted fracture of the proximal half of the left tibia and fibula. She was unconscious when admitted to hospital and although she recovered after a short time, she remained drowsy and irritable. Routine examination of the central nervous system revealed to an observant registrar a "hæmorrhage behind the pupil" and I was asked to give my opinion two days after the accident.

There was no other injury, apart from the fractures. The child had the irritable drowsiness that reminded me of tuberculous meningitis. The pupils were slightly dilated, reacted sluggishly to light, and their reaction was ill sustained. The ocular media were clear and the fundi showed an unusual picture. Radiating from the upper and nasal aspects of each disc were striate hæmorrhages. These coalesced near the disc but forked out towards the periphery for about two

disc diameters. In addition, many small striate hæmorrhages were scattered throughout each fundus although predominantly in the upper half. Near the periphery and in the region of the maculæ the hæmorrhages were oval or round. The configuration of these hæmorrhages probably depended on the density of the axons in the nerve-fibre layer of the retina. In addition, at the macula and at the periphery fluffy off-white " exudates " were seen. Hair-like hæmorrhages were present in the papillo-macular bundle. The fundi were observed for several days. The hair-like hæmorrhages in the papillo-macular bundle faded in 48 hours but new ones recurred for about 6 days after the accident. About this time the child's irritability and drowsiness disappeared and no new hæmorrhages were subsequently noted.

The whole clinical picture could only be explained by postulating multiple minute fat-embolic, although at no time was a rash observed and two examinations of the urine revealed no fat globules.

Bury General Hospital, Lancs. J. McLENACHAN.

DIAGNOSIS OF DIABETES

SIR,—In your leading article of Oct. 1 you refer to the findings of Reid [1] that 48% of 352 diabetics seen in Dundee had symptoms for more than four months when the disease was diagnosed and 20% had symptoms for more than a year. If these high percentages are general throughout the country there would indeed be complete justification for your view that " such a state of affairs should no longer be tolerated ". However, I wonder if the picture is really quite so dark as would appear from the figures you quote? My own corresponding figures in a study of 300 patients seen at the Royal Devon and Exeter Hospital [2] show that 27% had symptoms for more than four months at the time of diagnosis and 15% had symptoms for one year or more.

Further analysis of this series reveals that in 12 (4%) cases the onset was acute and the diagnosis was made within six days of the presenting symptoms. In 5 of these patients the exact day or even hour of onset was known. In 13% of diabetic patients symptoms preceded diagnosis by a period of from seven days to one month, and 18% had symptoms for more than one month and less than two months, while 14% had symptoms for more than two months and less than three months.

I would suggest, however, that all surveys based on personal interview or questionary are open to criticism as is evident from the fact that in approximately two-thirds of my cases the onset of symptoms was so insidious that the patient was unable to define this accurately, even to within a two-month period. An indefinite onset of this nature was recorded in 75% of patients over 40 years of age and in 78% of patients without ketonuria. It is in this particular group of older diabetic patients without ketosis that there is so often a long delay in diagnosis.

Your leader also states that " at present diabetes mellitus is usually diagnosed when the patient reports with symptoms due to the primary disorder or, in about 20% of cases, to complications of the disease ".[3] In 95% of the Exeter patients the presenting symptom was one of the accepted classical symptoms of diabetes—namely, polyuria, polydypsia, polyphagia, loss of strength, or loss of weight. All five symptoms were present in 19% of patients, occurring in 24% of cases with ketosis and 15% of cases without ketosis, and were reported over twice as often in patients under 40 as in those over 40. However, in 44% of diabetic patients the presenting symptoms were multiple and 46% of these symptoms were due to complications of the disease. There is certainly, as you say, a widespread tendency to misinterpret the symptoms of this disease. Those which you select as being particularly liable to misinterpretation accounted for a high proportion of presenting symptoms in this survey—thirst (48%), polyuria (15%), loss of weight (14%), visual impairment (6%), and pruritus vulvæ (in 27% of females over 16 years of age), and genital puritus in men (4%).

With regard to your statement that " some of the delay in diagnosis is doubtless due to imperfections in the practice of doctors who fail to test the urine when the clinical picture suggests diabetes ", I feel that it is only fair to mention that in 240 (80%) of 300 patients in this Exeter survey the diagnosis was made by the family doctor. 25 new cases presented as severe diabetic ketosis or coma and in only 5, simulating acute abdominal emergencies, was the condition not recognised before admission to hospital. In 12 (4%) cases symptomless glycosuria of diabetic origin was an incidental finding at a routine medical examination or when the patient was seen for an unrelated condition. The remaining 48 (16%) were first diagnosed in hospital. These patients attended with diabetic symptoms or complications although their nature had not been previously recognised.

As you say, there is no doubt that much of the delay in diagnosis is due to ignorance among the lay public. This view is confirmed by my findings that in only 2 of 300 diabetic patients was the diagnosis made before a doctor was consulted, and this was only so because in each case the patient's wife was a trained nurse and recognised the symptoms of the disease. As my survey was completed some five years ago it is possible that the lay public is now better informed through, for example, the medium of television.

May I emphasise that I do not wish to detract in any way from the views in your leading article concerning the fundamental importance of early diagnosis of diabetes, but I felt that, in fairness, one should point out that the figures quoted in support of your thesis may well not be representative of the country as a whole. A lowered incidence of the classical symptoms of this disease can be expected only if early diagnosis is achieved. One way of attaining this object would be to act upon the suggestion made by Dr. Joslin [4] almost forty years ago that every person should have the urine examined for glucose on his or her birthday.

Princess Margaret Hospital, Swindon. A. G. FREEMAN.

1. Reid, J. J. A. *Med. Offr*, 1960, **103**, 325.
2. Freeman, A. G. *Brit. med. J.* 1958, i, 1149.
3. Beaser, S. B. *New Engl. J. Med.* 1948, **229**, 765.
4. Joslin, E. P. *J. Amer. med. Ass.* 1921, **76**, 79.

Appointments

CHARLES, A. H., T.D., M.A., M.B. Cantab., F.R.C.S., F.R.C.O.G.: consultant gynæcologist, Royal National Orthopædic Hospital, London.
BEASLEY, ROSEMARY A., M.R.C.S., D.OBST.: assistant M.O.H. and school M.O., Coventry.
CARUANA, SALVINO, M.D. Lpool, D.T.M. & H., D.P.H.: assistant M.O., Cheshire.
DOWNSBROUGH, F. K., M.B. Leeds, D.M.R.D.: consultant radiologist (neuro-radiology), Derby group of hospitals.
FRYER, ADA M., M.B. Glasg., D.OBST.: assistant M.O.H. and school M.O., Coventry.
GILBERT, BASIL, M.R.C.S., D.P.H.: deputy M.O.H. and deputy principal school M.O., Sunderland.

East Anglian Regional Hospital Board

BANERJEE, M. S., M.B. Calcutta, D.G.O.: registrar in obstetrics and gynæcology, Norfolk and Norwich hospital group.
BLUMBERG, N. A., M.B. W'srand, F.R.C.S.: surgical registrar, Ipswich and East Suffolk hospitals.
DAY, GEORGE, M.A., M.D. Cantab.: consultant physician-superintendent, Mundesley Hospital.
GOSS, G. C. L., M.B. Lond.: registrar in psychiatry, Hellesdon Hospital.
LLOYD, A. T., M.B. Brist., D.P.M.: senior registrar in psychiatry, Fulbourn and Addenbrooke's hospitals.
MCKECHNIE, IAN, F.R.C.S.E: consultant orthopædic surgeon, Peterborough and Stamford hospital group.
MEHTA, J. S., M.B. Bombay: radiological registrar, Ipswich and East Suffolk Hospital.
PEARS, M. A., M.D. Lond., M.R.C.P.: consultant physician, King's Lynn hospital group.
VARSAMIS, I., M.B. Alexandria: registrar in psychiatry, St. Andrew's Hospital, Norwich.
WALLACE, SHEILA, M.B. Lond., D.OBST.: pædiatric registrar, Ipswich and East Suffolk Hospital.

Notes and News

INTERNATIONAL FEDERATION OF SURGICAL COLLEGES

THIS Federation was inaugurated in Stockholm in July, 1958, and some of its objects are to improve and sustain standards of surgery throughout the world, to maintain close relations among approved surgical colleges and institutions, and to maintain high standards of education, training, and research. At a meeting in Munich in September, 1959, working parties were established to examine the following subjects: surgical missions; training of surgeons; surgical research; and the interchange of young surgeons. A gathering of the Federation at the Royal College of Surgeons in London on Oct. 18–20 was attended by representatives of the 24 member institutions. It began with meetings of the working parties, and the later proceedings included two sessions on new research work, one contributed by the American College of Surgeons, and the other by the surgical colleges in the British Isles. Prof. Digby Chamberlain and Mr. Harold Edwards described the teaching of surgery as it was undertaken at the Royal College of Surgeons of England; and visitors were also able to see something of the postgraduate course organised by the Institute of Basic Medical Sciences and to inspect the scientific departments and museums of the college.

At a dinner on Oct. 19 in the Edward Lumley Hall of the college, the Minister of Health, Mr. Enoch Powell, proposed The Federation, and its president, Sir Harry Platt, responded. The president of the college, Sir Arthur Porritt, then formally admitted to honorary fellowship Prof. E. Dahl-Iversen, of Copenhagen, who was introduced by Prof. Ian Aird, and Prof. J. F. Nuboer, of Utrecht, who was introduced by Prof. Digby Chamberlain.

During the meeting the Duke of Edinburgh visited the college and took tea with the council of the Federation.

KYASANUR FOREST DISEASE

AT a meeting of the Royal Society of Tropical Medicine and Hygiene in London on Oct. 20, Dr. Telford H. Work presented a film entitled *Kyasanur Forest Disease in India* and gave a detailed commentary. The disease first appeared in southern India after many deaths had been noticed in December, 1955, among monkeys in the Kyasanur forest. The dead monkeys exhibited bleeding from the nose and anus, and when permission to shoot monkeys from the forest was obtained it was found that they invariably harboured ticks. Human cases of the disease were characterised by very sudden onset, high fever, headache, and great prostration. The fever, which usually lasted between five and twelve days, was associated with pronounced stiffness of the muscles of the neck and lumbar regions and, on or about the third day of the illness, with bleeding from the gums and tarry stools. Death when it occurred was usually between the seventh and tenth days of the fever, and necropsy revealed focal necrosis in the liver but no encephalitis. Among early cases the mortality was 28% but later this was reduced to 4–6%. The virus was isolated. It belongs to group B of the Arbor viruses and is transmissible by the ixodid ticks found on the monkeys, and a vaccine has now been prepared from it.

CANCER IMMUNISATION IN SWEDEN

IN the past two years clinical tests of a cancer vaccine and a cancer serum have been carried out at Radiumhemmet in Stockholm on inoperable cases. Preliminary reports by Dr. Bertil Björklund, who is in charge of the Immunological Research Laboratory in Stockholm, and by Dr. Lennart Malmquist, who is attached to Radiumhemmet, have appeared in *Svenska Läkartidningen* for Oct. 7. The vaccine is an antigen obtained from mass cultures in vitro of a cancer strain grown continuously for ten years. The serum was derived from horses immunised by antigens from necropsy material, and, more recently, also by purified antigen from in-vitro cell cultures. Only the active globulin fraction of the serum is given to the patient. Various dosages and modes of administration have been tried. The vaccine is given intracutaneously, and the serum intravenously and also by injection into the tumour. In two patients the serum provoked such violent pain in the tumour itself that the injection had to be discontinued and a narcotic administered intravenously. Five cases are reported in detail. Striking improvement was observed in several patients. Case 5 was typical: a patient born in 1899 was found in November, 1959, to have cancer of the gums and mouth. Radiotherapy proved ineffective, and in March, 1960, the case was considered inoperable. Serum and vaccine treatment was started in April, 1960. By the middle of May the tumour had notably regressed, and by June 3, 1960, it was held to be operable and was removed. The patient died ten days later of " circulatory insufficiency ". At necropsy no metastases were found.

The National Cancer Institute of the U.S. Public Health Service has made a grant to Radiumhemmet to promote this research.

THE RETREAT

TOWARDS its fund for reconstruction, this independent mental hospital has received nearly £150,000; and its new nurses' training school was opened by the Earl of Feversham on Sept. 19. Other additions made during the past year include a new men's admission ward. To bring the whole hospital correspondingly up to date will need a good deal more money, and donations, covenants, or legacies will be gratefully received by the treasurer, The Retreat, 107, Heslington Road, York.

In the 163rd annual report of the physician superintendent, Dr. C. C. Beresford says that in 1959 the average number of patients in residence was 236. As in other mental hospitals, this figure is about 10% lower than in the peak years of 1956–57; but admissions, at 404, remain high. Because more is done in outpatient departments and day hospitals the work of The Retreat becomes steadily more arduous. " The type of case that comes into hospital now is rarely the average straightforward disease but the atypical, complicated or severe example of it ". Dr. Beresford welcomes the present movement as a healthy one: " for far too long have many patients who could have been treated at home been obliged to enter a mental hospital or not receive any treatment at all ". Nevertheless, he is inclined to think that the tendency to treat people as outpatients whenever this is possible is going too far; and, if it goes further, a reaction will follow, with a bigger proportion of cases treated in hospital. " Certain illnesses in fact do far better in hospital. For example, one can cite the addiction neuroses, the senile psychoses, and those who have become ill because of intolerable environmental strain".

The scope of day treatment at the hospital has been enlarged, and the number of consultation centres has been extended. But Dr. Beresford believes that time will show that the need for an essentially residential treatment unit such as The Retreat is as great as ever. Thanks to the Mental Health Act, patients can now be admitted as to any other kind of hospital. " This may sound to many a trivial matter " but " in fact it is of the greatest importance . . ." The mental hospital is now allowed to admit any patient who does not refuse such treatment, without any of the previous formalities. It is hoped that eventually, under the new Act, the patient contending with his illness will no longer have to contend also with the legal and popular prejudices that went with it.

University of Oxford

On Oct. 13 the following degrees were conferred in absentia:

D.M.—P. D. Wall.
B.M.—Anne Stern.

University of Birmingham

The title of professor of physiological chemistry has been conferred on Dr. W. Y. Thorpe, formerly reader in chemical physiology.

University of Edinburgh

On Oct. 22 the degrees of M.B., CH.B. were conferred on Louise F. Fairley.

University of London

Mr. W. T. Irvine, reader in surgery at London Hospital Medical College, has been appointed to the chair of surgery at St. Mary's Hospital Medical School.

Mr. Irvine, who is 35 years of age, graduated B.SC. from the University of Glasgow in 1944 and M.B. in 1947. He held house-appointments before serving as a surgical specialist with the R.A.M.C. from 1950 to 1952. After spending a year as surgical registrar at the Western Infirmary, Glasgow, he became Archibald fellow in experimental surgery at McGill University. In 1955 he was awarded a Mayo Foundation fellowship in physiology at Rochester, Minnesota. In 1956 he returned to Glasgow and was appointed lecturer in surgery at the Western Infirmary. He took the degrees of CH.M. and M.D. of Glasgow both with honours. He has held the readership in surgery at the London Hospital since 1957. His published work includes papers on lymphosarcomata of the small intestine, late complications of uretero-colostomy, and the diathermy treatment of bladder papillomata. He has also published many papers on the mechanism of gastric secretion and on various aspects of gastro-enterology. Recently he has been responsible for introducing isolated perfusion techniques with cytotoxic agents using the heart-lung machine for advanced malignant conditions.

Dr. D. R. Laurence, senior lecturer at University College and University College Hospital Medical School, has been appointed to the readership in pharmacology and therapeutics at the College and School. The title of reader in tropical hygiene has been conferred on Dr. B. B. Waddy in respect of his post at the London School of Hygiene and Tropical Medicine.

University of Sheffield

Mr. S. D. Clarke has been appointed lecturer in surgery, Mr. D. G. Taylor part-time lecturer in cardiothoracic surgery, Mr. A. B. Nutt part-time lecturer in ophthalmic surgery, and Dr. R. S. Morton part-time lecturer in venereal diseases.

Royal College of Physicians of London

On Oct. 18 the Weber-Parkes prize was presented to Sir Geoffrey Marshall, and the Moxon medal to Professor John McMichael, F.R.S.

The Registrar said that Sir Geoffrey Marshall early developed an interest in chest disease and particularly tuberculosis, and with his appointment to Guy's Hospital this interest quickened and he attained a considerable reputation as a teacher. Early in the chemotherapeutic era he became chairman of the chemotherapy of tuberculosis trials committee of the Medical Research Council—work of the highest importance. He also took a leading part in the formation of the Association for the Study of Diseases of the Chest, later known as the Thoracic Society, and he became its president. He was later president of the Royal Society of Medicine. In his counselling and advice his example over the years had been and continued to be a great stimulus to his colleagues both young and old.

Presenting the Moxon medal, the Registrar emphasised Professor McMichael's prowess as a clinician, as a pioneer of modern scientific medicine, particularly concerned with investigations, and as an administrator. In the clinical field he had become a consultant's consultant. His pioneer work in cardiac catheterisation and percutaneous hepatic biopsy had been opposed and even condemned by more conservatively minded physicians. McMichael, however, had the vision to see that accuracy of diagnosis was in the best interests of his patients, and today these methods were used throughout the world. As an administrator, McMichael had played a very important part in the evolution and development of full-time university units in departments of medicine throughout Great Britain and in the Commonwealth. His experience and progressive views in this rapidly developing aspect of medical education were second to none. He was now an international figure of modern world medicine.

Royal Australasian College of Physicians

On Oct. 10 the following were admitted to the membership:

J. S. Duke, M. T. Havyatt, I. J. Mackie, F. L. Rothwell, G. S. Walker (New South Wales); J. K. Dawborn, J. E. Gault, B. C. Ritchie (Victoria); A. G. Collins, R. L. Hodge, D. A. Kennedy, T. A. White (South Australia); J. E. Edwards, John Ferguson, E. D. O'Callaghan (Queensland); D. H. Gutteridge (Western Australia).

Royal Medico-Psychological Association

On Friday, Nov. 18, at 2.15 P.M., at 1, Wimpole Street, London, W.1, Dr. Eliot Slater will give a Maudsley lecture. His subject will be Hysteria 311.

Royal College of Surgeons of Edinburgh

At the annual meeting of the college, held on Oct. 19, the following office-bearers were elected:

President, Prof. John Bruce; vice-presidents, Prof. Norman Dott and Mr. W. W. Galbraith; secretary, Mr. J. A. Ross; treasurer, Mr. J. J. Mason Brown; President's council, Mr. David Band, Dr. J. B. Dewar, Mr. I. L. Dick, Prof. D. M. Douglas, Mr. C. W. A. Falconer, Mr. A. J. C. Hamilton, Mr. J. N. Hartley, Prof. R. J. Kellar, Dr. R. G. Macbeth, Dr. D. S. Middleton, Prof. G. I. Scott, Mr. R. L. Stewart, Mr. T. I. Wilson; representative on the General Medical Council, Mr. K. Paterson Brown; conservator of museum, Prof. E. C. Mekie; hon. librarian, Sir Walter Mercer.

The following were admitted to the fellowship:

R. Hanif Ahmed, Raja Ghulam Asghar, Syed Abbas Askari, M. P. Awon, Manickavasagar Balasegaram, Fiona M. Bennett, R. K. Berry, D. E. Burgess, C. W. Packiaratnam Canagaretna, D. B. Chapman, S. D. Clarke, J. L. Clarke, J. L. Colvin, J. Y. Crooks, R. B. Davey, Venkatrao Dawle, J. A. S. Dickson, T. Satya Doss, E. I. P. Ebosie, E. A. Elebute, Sudhir Kumar Ghose, Sah Dev Gupta, Umesh Chandra Gupta, Khin Maung Gyi, K. I. M. Heath, Gurupprasad Sidhraj Hiremath, R. S. Hole, Daniel Hugo, J. A. Hyde, J. O'H. Hyde, H. B. S. Kemp, I. R. Kernohan, Indru Tekchand Khubchandani, Ram Partap Kumar, J. B. Laine, R. A. Leggatt, Greta I. Leitch, Franklin Wang-Pong Li, Gordon Low, Earl Ming-Teh Lu, D. J. McAuliffe, Jean M. M. McKenzie, J. H. McKessar, Madavilakom Padmanabhapillay Manomohan, Mohamed Abdel Kader Mohamed Mansour, M. D. Middleton, L. J. Phillips, P. A. M. Pozzi, Nagesh Mukund Prahbu, K. Alagamuthu Ramalingam, Mohini Vasanmal Ramchandani, Vinodray Dhirajlal Raval, D. M. Ritchie, Adnam Sarsam, I. G. Schraibman, Alan Simpson, J. W. Smith, M. G. H. Smith, Dhun Dinshaw Sumariwalla, G. R. Thoms, R. S. Todd, P. J. Venter, J. P. A. Weaver, D. G. Wray, I. W. M. Wright, Jayaraja Yogaratnam.

Faculty of Radiologists

On Nov. 19 and 20 at the Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2, this Faculty will hold a postgraduate weekend course. Further particulars may be had from the secretary of the Faculty, 47, Lincoln's Inn Fields, W.C.2.

On Friday, Nov. 18, at 4.30 P.M., at the Royal College of Surgeons, Prof. R. W. Scarff will give a Skinner lecture on prognosis in carcinoma of the breast.

Royal National Throat, Nose, and Ear Hospital, London

The trustees of the Nuffield Foundation have increased from £60,000 to £100,000 their grant for the erection of the Nuffield hearing and speech centre attached to this hospital. Building work is expected to begin early next year.

National Society of Children's Nurseries

On Thursday, Nov. 10, at 10.15 A.M., at County Hall, London, S.E.1, this society will hold a conference on Working Wives—What of the Children? The speakers will include Dr. W. Lumsden Walker, Dr. Bryan Reffold, and Dr. David Morris.

Genetics, Statistics, and Radioisotopes

The Institute of Basic Medical Sciences will hold a course on this subject on Monday, Oct. 31, and Nov. 1 and 2. Further particulars may be had from the secretary of the Institute, Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2.

College of General Practitioners

Public Welfare Foundation Prize.—This competition (six prizes of £40) is designed to encourage senior medical students in the United Kingdom and Eire who have taken advantage of opportunities to discuss the diagnosis and management of patients in the setting of general practice. Details may be had from the dean of the students' medical school or from the secretary of the college, 41, Cadogan Gardens, London, S.W.3.

Rockefeller Foundation

During the third quarter of 1960 the Foundation made grants of over $2 million. Those for medical and natural sciences amounted to over $1 million. These include a five-year grant of $43,500 for research in human genetics under Prof. L. S. Penrose at University College, University of London, and a three-year grant of $30,000 for the continuation of work on the ultrastructure of nucleic acids, the fine structure of muscle, and the chemical behaviour of chromosomes under Prof. J. T. Randall at King's College, University of London.

Mr. J. F. Hunt has been appointed controller of supplies at the Ministry of Health in succession to Mr. A. D. Campbell who is retiring.

On Wednesday, Nov. 2, at 5.15 P.M., at the Royal Free Hospital, Gray's Inn Road, London, W.C.1, Dr. F. J. W. Miller will speak on the Thousand Families Survey.

At a meeting of the Medical Electronics Discussion Group on Friday, Nov. 4, at 6 P.M., at the Institution of Electrical Engineers, Savoy Place, London, W.C.2, there will be a discussion on electro-convulsive therapy. The opening speakers will be Dr. A. Spencer Paterson and Mr. W. H. Stanton.

A meeting for general practitioners will be held on Sunday, Nov. 6, at 10.15 A.M., at University College Hospital, London, W.C.1. Prof. A. S. Prophet will speak on dental emergencies in general practice.

On Wednesday, Nov. 9, at 8.15 P.M., at the General Infirmary at Leeds, the Yorkshire Society of Anæsthetists will hold a symposium on the North American Anæsthetic Scene. The speakers will be Dr. R. P. Harbord, Dr. Gwendolen Harrison, and Dr. F. G. Mackintosh.

The Royal College of Nursing has received from the Privy Council the orders in council allowing the necessary alterations to its royal charter and by laws to extend its membership to male nurses. From Nov. 1 men and women holding the qualification of State-registered nurse, registered mental nurse, registered nurse for mental defectives, registered nurse for sick children, and registered fever nurse will be eligible for membership.

The 1960–61 programme of Galenicals, the student society of the School of Medicine of the University of Bristol, will include the following addresses: Sir Robert Macintosh, An Anæsthetist in the U.S.S.R. and China, Nov. 4; Dr. R. E. Hemphill, Psychological Disorder and the Artist (presidential address), Nov. 18; Dr. Richard Asher, The Sins of Medical Students, Dec. 2; Dr. Macdonald Critchley, The Medical Aspects of Oscar Wilde, Jan. 20; Prof. R. C. Browne, My Experience in a University Department of Industrial Health, Feb. 17; Mr. Norman Lake, The Effects of Low Temperature and Resuscitation on Living Tissues, March 3; Sir Henry Dale, the Royal Society of London and Medical Science—a record of 300 years, March 17. The secretary of the society is Mr. A. J. G. Dickens, Students' Common Room, Bristol Royal Infirmary, Bristol, 2.

The annual dinner of the Glasgow University Club, London, will be held at the Trocadero Restaurant, London, W.1, at 7.30 P.M. on Thursday, Nov. 10. Particulars may be had from Dr. J. F. Heggie, department of pathology, North Middlesex Hospital, N.18.

A semi-permanent exhibition will be held at the Institute of Dermatology, Lisle Street, London, W.C.2, from Nov. 7 to 30, by Dr. P. D. Samman on cutaneous tuberculosis and sarcoidosis.

The National Corporation for the Care of Old People has compiled a register of research that is being done on social and sociomedical aspects of the welfare of the elderly. Only work that has been in progress since 1955 has been included. Copies of the register (10s. post free) may be had from the Corporation, Nuffield Lodge, Regent's Park, London, N.W.1.

Diary of the Week

OCT. 30 TO NOV. 5

Sunday, 30th

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
10.15 A.M. Mr. S. E. Birdsall: Common Ear, Nose, and Throat Conditions.

Monday, 31st

POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W.12
4 P.M. Dr. Wilfred Sircus: Practical Application of Gastric Secretion Studies.

INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
4.30 P.M. (Queen Charlotte's Maternity Hospital, Goldhawk Road, W.6.) Mr. G. W. Garland: Antenatal Supervision.

Tuesday, 1st

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Mr. N. H. Porter: Physiological Study of the Pelvic Floor Muscles in Rectal Prolapse. (Arris and Gale lecture.)

UNIVERSITY OF LONDON
5.15 P.M. (Middlesex Hospital Medical School, Mortimer Street, W.1.) Prof. Hans Schaefer (Heidelberg): Principles of Circulatory Regulation. (First of two lectures.)

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Prof. Michael Stoker: Latent Virus Infections.

ST. MARY'S HOSPITAL MEDICAL SCHOOL, W.2
5 P.M. (Wright Fleming Institute.) Mr. Elliot Philipp: Antepartum Hæmorrhage.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W.1
5.30 P.M. Dr. H. C. Grant: Chronic Meningitis.

INSTITUTE OF DERMATOLOGY, LISLE STREET, W.C.2
5.30 P.M. Dr. A. D. Porter: Keratinisation, Normal and Abnormal.

LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5.15 P.M. (General Infirmary at Leeds.) Dr. W. Ritchie Russell: Neurological Aspects of Memory.

Wednesday, 2nd

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M. Dr. J. B. Enticknap: Coronary Thrombosis and Other Forms of Ischæmic Heart Disease. (Erasmus Wilson demonstration.)

UNIVERSITY OF LONDON
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Dr. Charles Wilcocks: Aspects of Medical Investigation in Africa. Tuberculosis. (First Heath Clark lecture.)

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5.15 P.M. *History of Medicine.* Sir Philip Manson-Bahr: Malaria Story.

POSTGRADUATE MEDICAL SCHOOL
2 P.M. Prof. R. H. S. Thompson: Biochemistry of Multiple Sclerosis.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W.1
3.30 P.M. Mr. F. Ward: Flammability of Textiles.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. Arthur Tickner: Biochemistry of Pigmentation.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. W. D. W. Brooks: Spontaneous Pneumothorax.

LONDON AMATEUR BOXING ASSOCIATION
8 P.M. (British Railways Film Unit, Savile Row, W.1.) Dr. J. L. Blonstein: Olympic Games in Retrospect.

ASSURANCE MEDICAL SOCIETY
5 P.M. (11, Chandos Street, W.1.) Mr. R. E. Beard: Thoughts on Mortality, Morbidity, and Medical Underwriting.

MIDLAND MEDICAL SOCIETY
8.30 P.M. (Joint meeting with Midland Counties Veterinary Association, Birmingham Medical Institute, 36, Harborne Road, Edgbaston.) Dr. J. Deans Rankin, Dr. K. B. Rogers: Diseases of Animals Communicable to Man.

MANCHESTER MEDICAL SOCIETY
4.30 P.M. (Medical School, University of Manchester.) *Medicine.* Dr. C. J. Hodson: Radiological Observations on the Natural History of Chronic Pyelonephritis.

UNIVERSITY OF LEEDS
5 P.M. (General Infirmary at Leeds.) Mr. D. W. Currie: Cancer of the Female Genital Tract.
6 P.M. Mr. Herbert Agar: General Surgical Problems in Gynæcology.

MEDICO-CHIRURGICAL SOCIETY OF EDINBURGH
8.30 P.M. (Royal College of Surgeons of Edinburgh, 18, Nicolson Street.) Prof. R. B. Hunter: Therapeutics 1960.

Thursday, 3rd

ROYAL COLLEGE OF PHYSICIANS, Pall Mall East, S.W.1
5 P.M. Dr. W. I. Card: Concept of Gastric Secretory Cell Mass. (Bradshaw lecture.)

UNIVERSITY OF LONDON
5 P.M. (1, Wimpole Street, W.1.) Dr. Paul H. Holinger (Chicago): Clinical Aspects of Congenital Anomalies of the Larynx, Trachea, Bronchi, and Œsophagus. (Semon lecture.)
5.15 P.M. (Middlesex Hospital Medical School.) Professor Schaefer: Theory and Interpretation of the Electrocardiogram. (Second of two lectures.)
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Dr. Wilcocks: Aspects of Medical Investigation in Africa—Schistosomiasis. (Second Heath Clark lecture.)

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Dr. K. M. Rundall: Regular Folds in Protein and Polysaccharide Chains.

INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, S.E.5
5.30 P.M. Dr. Catherine Hebb: Intracellular Structures and Transmitter Substances in the Nervous System.

NUFFIELD ORTHOPÆDIC CENTRE, Oxford
8.30 P.M. Mr. H. V. Crock: Experiments on Spinal Fusion in the Dog.

NORTH WESTERN THORACIC SOCIETY
5 P.M. (Aintree Hospital, Liverpool.) Dr. John Howell, Dr. C. M Ogilvie: Physiological and Clinical Aspects of "CO_2 Retention"

HONYMAN GILLESPIE LECTURE
5 P.M. (University New Buildings, Teviot Place, Edinburgh.) Prof. J. H Kellgren: Osteoarthrosis in Patients and Populations.

Friday, 4th

ROYAL SOCIETY OF MEDICINE
10.30 A.M. *Otology.* Mr. J. P. Monkhouse: Triumphs and Problems of Middle-ear Surgery. (Presidential address.)
2.30 P.M. *Laryngology.* Mr. J. H. Otty: Retrospect and Prospect. (Presidential address.)
4 P.M. *Anæsthetics.* (Royal College of Surgeons.) Dr. R. M. Smith (Boston): Anæsthesia for Emergency Procedures in Children.

POSTGRADUATE MEDICAL SCHOOL
10 A.M. Mr. K. C. McKeown: Gastrectomy in Peptic Ulcer.
4 P.M. Dr. B. E. C. Nordin: Osteomalacia and Osteoporosis.

CIBA FOUNDATION
5 P.M. (66, Portland Place, W.1.) Prof. J. Konorski (Warsaw): Changing Concepts Concerning Physiological Mechanisms of Animal Motor Behaviour.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY
3.30 P.M. Dr. Imrich Friedmann: Advances in Chemotherapy.

INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
3 P.M. (Chelsea Hospital for Women, Dovehouse Street, S.W.3.) Prof. E. C. Amoroso: Endocrinology of Pregnancy.

ASSOCIATION OF ANÆSTHETISTS OF GREAT BRITAIN AND IRELAND
9.15 A.M. (Royal College of Surgeons.) Opening of two-day meeting.

PLYMOUTH MEDICAL SOCIETY
8.30 P.M. (North Friary House.) Mr. G. L. Alexander: Danger Signs in Cases of Head Injury.

Saturday, 5th

INSTITUTE OF LARYNGOLOGY AND OTOLOGY
NOON. Dr. Holinger: Endoscopy in Otolaryngic Pathology.